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## Original Communications

### THE SUBSTITUTION OF OLIVE OIL FOR BUTTER FAT IN INFANT FEEDING


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RECENTLY Holt, Tidwell, and Kirk[3] have reported their observations on the absorption of a number of fats introduced into infants' formulas. The size of globules, melting point, and chemical composition as factors were included in their study. This research developed a definite relationship between the degree of saturation of a fat (iodine value) and its absorption. Those with the higher iodine value were more completely absorbed. If fats containing long chain fatty acids were arranged according to iodine number, those with the higher values showed the more complete absorption. The absorption from a mixed fat feeding was found to be precalculable with fair accuracy, if its percentage of various unsaturated and saturated fats were known. Fecal lipids were quantitatively more saturated than the fats ingested. A greater percentage of the saturated fats were extruded in the stools. In accord with this observation, olive oil with a number of approximately 90 was found to be better absorbed than butter fat with a number of about 35. The knowledge that fats other than those found in milk, were more completely absorbed, presented a new phase in infant feeding.

To determine clinically the effect of fat substitution suggested by this research, a series of premature and newborn infants were fed a mixture, in which olive oil replaced butter fat. The food was a powder with a percentage composition approximately as follows: skim milk 40.6 per cent, virgin olive oil 17.5 per cent, dextrimaltose 31.7 per cent, calcium caseinate 10.1 per cent, mineral ash 3.0 per cent and halibut liver oil 0.1 per cent. It had a caloric value of 134 per ounce (3½ level tablespoons). In reliquefying for feeding, 1 ounce of powder added to


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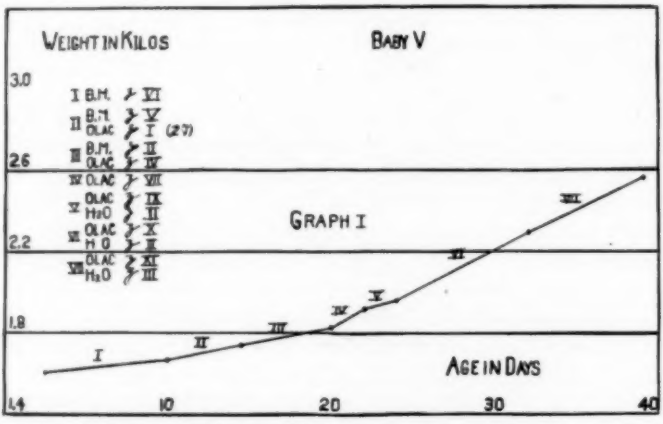
4 ounces of water was used to produce a food with 27 calories (per fluid ounce) and 1 ounce added to 6 of water to produce one with a value of 19 calories. The 27 calorie reliquefication had the following approximate composition: protein 4.7 per cent, fat 3.7 per cent, mineral ash 0.7 per cent, carbohydrate 10.7 per cent, moisture 80.2 per cent; and the 19 calorie product approximately, protein 3.3 per cent, fat 2.6 per cent, mineral ash 0.5 per cent, carbohydrate 7.6 per cent, moisture 86.0 per cent.

Graphs I, II, and III are records of the formulas and results as evidenced by weight increase in individual premature infants. Graph I is that of an infant started with breast milk, then complemented with olac,* and later put on olac alone. Graphs II and III are of premature infants fed from birth on olac alone. The premature babies were kept



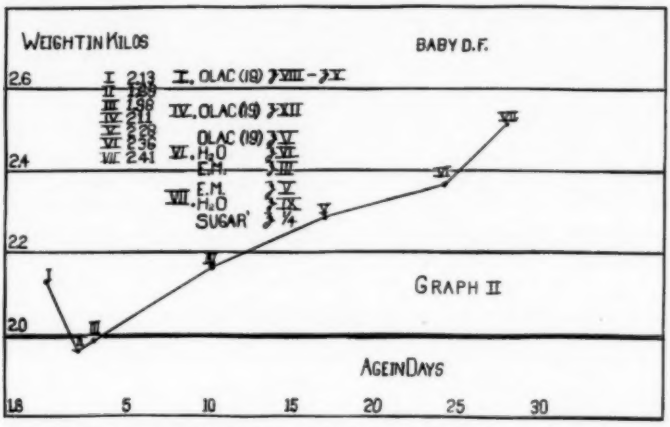

Graph I—B. M. (Breast Milk) recorded in ounces. Roman numerals on graph line indicate period during which corresponding formula was fed.

on this diet until they approached the 2,500 gram weight, at which point they were changed to their "discharge formula." This change was made at the hospital because "graduate prematures" were not controlled by our station after discharge. They fell under the jurisdiction of the Chicago Department of Health. When the mother's milk was not available, evaporated milk was commonly ordered in the home by the health department physicians, and it seemed less dangerous to make this radical change under hospital observation.

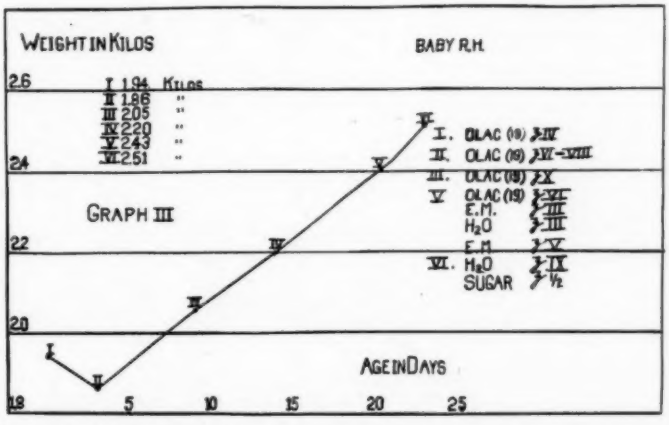
The series of 27 premature infants, Table I, were fed the olive oil substitute formulas according to 4 routines. The first group, Nos. 1 to 8 (Table I), was first fed breast milk alone (cases 7 and 8) or breast milk combined with dextrimaltose, evaporated milk, or olac. Later all

*This product, under the name, olac, was made available through the courtesy of Mead Johnson and Company.

their formulas were complemented with olac. These infants varied in birth weight from 1,612 to 2,122 grams. Their average gain per day on the combined feeding regimen was 12.7 grams. In comparison with similar infants on human milk alone, this gain is considered satisfactory.




Graph II—E. M. (Evaporated Milk) recorded in ounces. Roman numerals on graph line indicate date upon which corresponding formula was begun.




Graph III—E. M. (Evaporated Milk) recorded in ounces. Roman numerals on graph line indicate date upon which corresponding formula was begun.

The second group, Nos. 9 to 13 (Table I), was fed breast milk as their initial formulas, save in case 12, to which olac was added. In the next phase in this group breast milk was complemented with olac and finally olac was completely substituted. Their average gain while on the combination of olac and breast milk was 17.3 grams. The range in birth weights of these babies was from 1,584 to 2,207 grams. They remained

TABLE I

OLAC AS A COMPLEMENTARY AND SUBSTITUTE FOOD FOR PREMATURE INFANTS

| | | | | | COMPLEMENTARY OLAC | | | | | | | OLAC ALONE | | | | | | | CONDITION | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NO. | RACE | SEX | BIRTH OR ADM. WT. GM. | INITIAL FORMULA OZ. | AGE IN DAYS | INITIAL FORMULA OZ. | WEIGHT IN GM. START | WEIGHT IN GM. FINISH | TOTAL GAIN GM. | NO. OF DAYS | GAIN PER DAY GM. | AGE IN DAYS | INITIAL FORMULA OZ. | WEIGHT IN GM. START | WEIGHT IN GM. FINISH | TOTAL GAIN GM. | NO. OF DAYS | GAIN PER DAY GM. | ADMISSION | DISCHARGE | REMARKS |
| 1 | C | M | 2122 | BM-7<br>DM-⅛ | 3 | BM-7<br>Olac-6<br>$H_2O$-2<br>DM-⅛ | 2151 | 2545 | 394 | 28 | 14.0 | | | | | | | | Good | Good | |
| 2 | C | M | 2037 | BM-8<br>Olac-2 | 1 | BM-8<br>Olac-2 | 2037 | 2437 | 400 | 23 | 17.3 | | | | | | | | Fair | Good | |
| 3 | W | F | 1726 | BM-3<br>EM-3<br>$H_2O$-4<br>DM-¼ | 15 | Olac-2<br>EM-3<br>$H_2O$-5<br>DM-⅜ | 2215 | 2430 | 215 | 43 | 5.0 | | | | | | | | Good | Good | |
| 4 | W | M | 1934 | BM-6<br>EM-2<br>$H_2O$-2 | 7 | Olac-4<br>EM-3<br>$H_2O$-5<br>DM-½ | 2045 | 2599 | 554 | 26 | 21.3 | | | | | | | | Good | Good | |
| 5 | C | M | 1612 | BM-8<br>DM-⅛ | 7 | BM-7<br>Olac-1<br>$H_2O$-2<br>DM-⅛ | 1718 | 2410 | 692 | 51 | 13.5 | | | | | | | | Good | Good | |
| 6 | W | M | 2094 | BM-2<br>EM-4<br>$H_2O$-5<br>DM-¼ | 5 | EM-4<br>Olac-2<br>$H_2O$-8<br>DM-⅛ | 2272 | 2802 | 530 | 27 | 19.6 | | | | | | | | Fair | Good | Cyanosis |
| 7 | W | M | 2009 | BM-6 | 2 | BM-6<br>Olac-1 | 2071 | 2305 | 234 | 27 | 8.6 | | | | | | | | Good | Good | |
| 8 | W | M | 2088 | BM-6 | 17 | BM-9<br>Olac-1 | 2190 | 2215 | 25 | 10 | 2.5 | | | | | | | | Good | Good | |
| AVERAGE—(CASES 1-8) | | | | | | | | | | 29 | 12.7 | | | | | | | | | | |

TABLE I—CONT'D

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | C | F | 1775 | BM-5 | 13 | BM-8<br>Olac-1 | 1918 | 2020 | 102 | 6 | 17.0 | 19 | Olac-8<br>$H_2O$-2 | 2020 | 2390 | 370 | 17 | 21.7 | Good | Good | |
| 10 | W | F | 1584 | BM-5 | 10 | BM-8<br>Olac-1 | 1860 | 2180 | 320 | 17 | 18.8 | 27 | Ol*-7 | 2180 | 2485 | 305 | 13 | 23.4 | Good | Good | Syphilis |
| 11 | W | F | 1839 | BM-6 | 10 | BM-5<br>Olac-1 | 1889 | 2090 | 201 | 6 | 33.5 | 16 | Olac-8 | 2090 | 2470 | 380 | 24 | 15.8 | Good | Good | |
| 12 | C | M | 2207 | BM-10<br>Olac-2 | 1 | BM-10<br>Olac-2 | 2207 | 2244 | 37 | 8 | 4.6 | 8 | Olac-15 | 2244 | 2595 | 351 | 38 | 9.2 | Good | Good | |
| 13 | C | M | 1740 | BM-6 | 28 | BM-2<br>Olac-6<br>EM-1<br>DM-¼ | 2159 | 2275 | 116 | 9 | 12.8 | 37 | Olac-8<br>$H_2O$-2 | 2275 | 2505 | 230 | 16 | 14.3 | Good | Good | |
| AVERAGE—(CASES 9-13) | | | | | | | | | | 9 | 17.3 | | | | | | 21 | 16.8 | | | |
| 14 | C | F | 1839 | BM-7 | | | | | | | | 6 | Ol*-8 | 1932 | 2795 | 863 | 23 | 37.5 | Good | Good | |
| 15 | W | M | 1924 | BM-6 | | | | | | | | 2 | Olac-8 | 1994 | 2510 | 516 | 17 | 30.3 | Good | Good | |
| 16 | C | M | 1789 | BM-5 | | | | | | | | 2 | Olac-7 | 1795 | 2495 | 700 | 33 | 21.2 | Good | Good | |
| 17 | W | F | 2187 | BM-6 | | | | | | | | 2 | Olac-6 | 2208 | 2386 | 178 | 16 | 11.1 | Good | Good | |
| 18 | C | M | 2045 | BM-5 | | | | | | | | 2 | Olac-5 | 2110 | 2442 | 332 | 20 | 16.6 | Good | Good | |
| AVERAGE—(CASES 14-18) | | | | | | | | | | | | | | | | | 22 | 23.3 | | | |
| 19 | W | M | 1839 | Olac-4 | | | | | | | | 1 | Olac-4 | 1839 | 2465 | 626 | 41 | 15.2 | Good | Good | |
| 20 | W | M | 2164 | Olac-5 | | | | | | | | 1 | Olac-5 | 2164 | 2390 | 226 | 39 | 5.7 | Good | Good | |
| 21 | W | M | 2102 | Olac-4 | | | | | | | | 1 | Olac-4 | 2102 | 2379 | 277 | 17 | 16.2 | Good | Good | |
| 22 | W | F | 2017 | Olac-4 | | | | | | | | 1 | Olac-4 | 2017 | 2495 | 478 | 34 | 14.0 | Good | Good | |
| 23 | W | M | 2201 | Olac-5 | | | | | | | | 1 | Olac-5 | 2201 | 2260 | 59 | 15 | 3.9 | Good | Good | Diarrhea<br>Pyocyaneus<br>infection |
| 24 | C | M | 2045 | Olac-5 | | | | | | | | 1 | Olac-5 | 2045 | 2310 | 265 | 17 | 15.6 | Good | Good | |
| 25 | W | M | 2073 | Olac-5 | | | | | | | | 1 | Olac-5 | 2073 | 2272 | 199 | 11 | 18.9 | Good | Good | |
| 26 | W | M | 2073 | Olac-4 | | | | | | | | 1 | Olac-4 | 2073 | 2160 | 87 | 13 | 6.6 | Good | Good | |
| 27 | W | F | 1995 | Olac-4 | | | | | | | | 1 | Olac-4 | 1995 | 2102 | 207 | 20 | 10.3 | Good | Good | |
| AVERAGE—(CASES 19-27) | | | | | | | | | | | | | | | | | 22 | 11.8 | | | |
| AVERAGE—(CASES 1-27) | | | | | | | | | | 19 | 15.0 | | | | | | 21.5 | 16.3 | | | |

*Caloric value 27 per ounce.

All other olac formulas are 19 calories per ounce.

TABLE II

DETAIL AND RESULTS OF OLAC FEEDING IN THE NEWBORN

| NO. | RACE | SEX | BIRTH WT. OR ADM. WT. GM. | AGE IN DAYS WHEN STARTED | INITIAL FORMULA | INITIAL CAL./ KG. BODY WT. | UNDER OBSERVATION DAYS | FINAL FORMULA | FINAL CAL./ KG. BODY WT. | WEIGHT IN GM. | | TOTAL GAIN IN GM. | GAIN PER DAY IN GM. | CONDITION | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | START | FINISH | | | START | FINISH | |
| 1 | W | M | 3125 | 14 | Olac(19) 15<br>$H_2O$ 6 | 87.0 | 73 | Olac(27) 30 | 150.0 | 3267 | 5398 | 2131 | 29.1 | Good | Good | |
| 2 | W | F | 3366 | 16 | Olac(19) 21 | 118.0 | 112 | Olac(27) 27 | 118.5 | 3366 | 6150 | 2784 | 24.8 | Good | Good | |
| 3 | W | M | 3054 | 14 | Olac(19) 10<br>$H_2O$ 11 | 65.7 | 84 | Olac(27) 24 | 114.2 | 2897 | 5671 | 2774 | 33.0 | Good | Good | |
| 4 | W | M | 2777 | 28 | Olac(19) 11<br>$H_2O$ 10 | 67.2 | 68 | Olac(27) 30 | 110.6 | 3110 | 7329 | 4219 | 62.0 | Good | Fair | Trsf. to Cook Co.—Broncho-pneumonia, recovered |
| 5 | W | M | 3153 | 9 | Olac(19) 10<br>$H_2O$ 11 | 60.3 | 106 | Olac(27) 30 | 168.0 | 3153 | 4829 | 1676 | 15.8 | Good | Fair | Trsf. to Cook Co.—Bilat. Otitis, recovered |
| 6 | W | F | 3750 | 12 | Olac(19) 11<br>$H_2O$ 13 | 56.6 | 93 | Olac(27) 30 | 130.8 | 3693 | 6193 | 2500 | 26.8 | Good | Good | |
| 7 | W | M | 3792 | 24 | Olac(19) 10<br>$H_2O$ 14 | 50.1 | 115 | Olac(27) 30 | 102.6 | 3792 | 7897 | 4105 | 35.7 | Good | Good | |
| 8 | C | F | 2826 | 3 | Olac(19) 6<br>$H_2O$ 12 | 40.4 | 101 | Olac(27) 30 | 154.2 | 2826 | 5255 | 2429 | 24.0 | Good | Good | |
| 9 | W | M | 3380 | 4 | Olac(19) 14<br>$H_2O$ 10 | 75.8 | 109 | Olac(27) 27 | 121.0 | 3522 | 6022 | 2500 | 22.9 | Good | Good | |
| 10 | W | F | 3045 | 9 | Olac(19) 14<br>$H_2O$ 6 | 87.5 | 96 | Olac(27) 24<br>$H_2O$ 9 | 141.7 | 3045 | 4573 | 1528 | 15.9 | Good | Good | |
| 11 | C | M | 2727 | 2 | Olac(19) 6<br>$H_2O$ 12 | 41.9 | 112 | Olac(27) 24 | 119.5 | 2727 | 5426 | 2699 | 24.0 | Good | Good | |
| 12 | W | M | 2613 | 10 | Olac(19) 6<br>$H_2O$ 12 | 43.6 | 73 | Olac(27) 24 | 159.1 | 2613 | 4076 | 1463 | 20.0 | Fair | Good | |
| Average | | | | | | 66.1 | 95 | | 132.5 | 3167 | 5734 | 2567 | 27.8 | | | |

on olac alone from 13 to 38 days. Their average gain on olac was 16.8 grams per day. This was approximately the same as on equal caloric values of olac and breast milk.

The third group, Nos. 14 to 18 (Table I), was given breast milk for from 2 to 6 days and then changed directly to olac. Their birth weights ranged from 1,789 to 2,187 grams. They remained on olac for from 16 to 33 days and their average gain per day while on this food was 23.3 grams, well above our expectancy on breast milk.

The fourth group, premature infants Nos. 19 to 27 inclusive (Table I), was placed on olac with a caloric value of 19 per ounce, as the initial formula. The fact is stressed that this group received no human milk at any time. A single feeding of breast milk changes the gastrointestinal flora, an important factor in premature feeding. The range in birth weight of these babies was from 1,839 to 2,201 grams. They remained on olac alone for from 11 to 41 days and their average gain per day was 11.8 grams, slightly below our usual average.

The average gain for groups 2, 3 and 4 (19 premature infants) during the period they were fed olac only was 16.1 grams per day, with a maximum gain of 37.5 and a minimum of 3.9. Their period of observation averaged 21.5 days, with a minimum of 11 and a maximum of 41 days.

Premature infants numbers 10 and 14 received olac with a value of 27 calories per ounce. Both made excellent gains with no gastrointestinal upsets. All of the others received the mixture with a value of 19 calories per ounce. Halibut liver oil was added to all formulas beginning on the first day, and orange juice at the end of the first week.

In the study of normal newborn infants, alternate children were selected upon admittance to St. Vincent's Infant and Maternity Hospital. The initial feeding of the problem group was with olac (caloric value—19 per fluid ounce). As the infants increased in age and weight, the caloric value of the mixture was gradually increased to 27 per ounce. At the time olac was begun, their weights varied from 2,613 to 3,792 grams. Their average gain per day was 27.8 grams for an average of 95 days. The control series of infants, Table III, chosen to simulate the research group as closely as possible in age, sex, and weight, were fed nonirradiated evaporated milk. Their weights when started on the problem varied from 2,613 to 4,367 grams. Their average gain per day was 15.4 grams for an average of 78 days.

No gastrointestinal disturbances which could be attributed to the food occurred in either group. In a few children in both groups, upper respiratory infection was accompanied by diarrhea. These were treated by reduction in diet, but in no instance by removal of olac. Orange juice and cod liver oil were included in the diet of both groups in the first month. None of the children received any other supplementary food during the period of observation.

Of the infants studied, 12 of the research group, and 10 of the control group were observed for a sufficient length of time and with an adequate

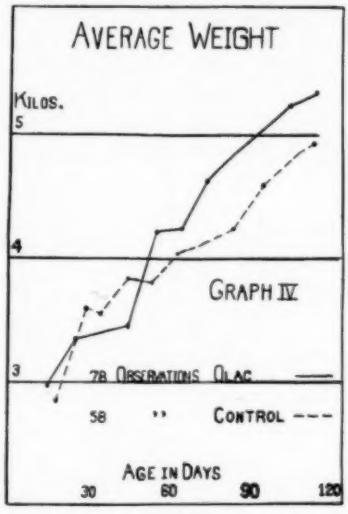
TABLE III

DETAIL AND RESULTS OF CONTROL FEEDING IN NEWBORN

| NO. | RACE | SEX | BIRTH WT. OR ADM. WT. GM. | AGE IN DAYS WHEN STARTED | INITIAL FORMULA | INITIAL CAL./ KG. BODY WT. | UNDER OBSERVATION DAYS | FINAL FORMULA | FINAL CAL./ KG. BODY WT. | WEIGHT IN GM. | | TOTAL GAIN IN GM. | GAIN PER DAY IN GM. | CONDITION | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | START | FINISH | | | START | FINISH | |
| 1 | W | M | 2613 | 11 | EM 5<br>DM 2T<br>$H_2O$ 13 | 98 | 72 | EM 10<br>$H_2O$ 20<br>DM 4T | 119 | 2613 | 4388 | 1775 | 24.6 | Good | Good | |
| 2 | W | M | 4367 | 9 | EM 8<br>$H_2O$ 9<br>DM 3T | 93 | 90 | EM 10<br>$H_2O$ 20<br>DM 3½T | 95 | 4367 | 5226 | 859 | 9.5 | Good | Good | |
| 3 | W | F | 3309 | 9 | EM 5<br>$H_2O$ 16<br>DM 2T | 77 | 80 | EM 10<br>$H_2O$ 20<br>DM 4T | 111 | 3309 | 4630 | 1321 | 16.5 | Good | Good | |
| 4 | W | M | 3039 | 9 | EM 5<br>$H_2O$ 13<br>DM 2T | 85 | 92 | EM 9<br>$H_2O$ 18<br>DM 4T | 124 | 3039 | 3801 | 762 | 8.4 | Good | Good | |
| 5 | W | F | 2635 | 8 | EM 6<br>$H_2O$ 12<br>DM 1T | 103 | 96 | WLAM 17T<br>$H_2O$ 30<br>DM 3½T | 119 | 2635 | 4346 | 1711 | 17.8 | Fair | Good | |
| 6 | W | M | 4346 | 23 | EM 6<br>$H_2O$ 24<br>DM 3T | 75 | 67 | EM 11<br>$H_2O$ 18<br>DM 5T | 118 | 4346 | 4901 | 555 | 8.2 | Good | Good | |
| 7 | W | F | 2244 | 56 | EM 4<br>$H_2O$ 12<br>DM 2T | 97 | 52 | EM 10<br>$H_2O$ 20<br>DM 4T | 128 | 2244 | 4005 | 1761 | 33.8 | Good | Good | |
| 8 | W | F | 3089 | 23 | EM 5<br>$H_2O$ 16<br>DM 3T | 94 | 66 | EM 10<br>$H_2O$ 19½<br>DM 4T | 115 | 3089 | 4445 | 1356 | 20.5 | Good | Good | |
| 9 | W | M | 3522 | 17 | EM 6<br>$H_2O$ 15<br>DM 3T | 92 | 73 | WLAM 6 oz.<br>SLAM 6 oz.<br>DM ½T | 143 | 3522 | 3891 | 369 | 5.0 | Good | Good | |
| 10 | W | F | 3600 | 14 | EM 5<br>$H_2O$ 15<br>DM 2T | 70 | 90 | EM 12<br>$H_2O$ 14<br>DM 5½T | 140 | 3600 | 4501 | 901 | 10.0 | Good | Good | |
| Average | | | | | | 88.4 | 77.8 | | 121.2 | 3276 | 4413 | 1137 | 15.43 | | | |

number of measurements, to be tabulated. The graphs were based on a total of 78 observations on the research and 58 on the control series. No infant was included whose period on the problem was less than 60 days. The maximum period of observation without additional food was 115 days. The primary observations of the olac group were made after having been fed this formula 14 days. None of the 12 children was over one month of age when olac was started, and nine of the 12 were 14 days or under. Formulas were well taken by both groups and none refused either mixture.

In the study of the growth and development of these newborns, we attempted to select those anthropometric measurements most commonly used. These included observations of weight, height, circumference of




Graph IV

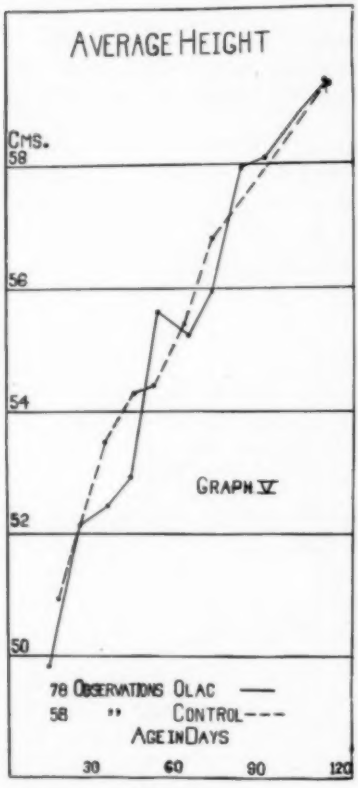
the head, circumference of the chest, and bi-iliac diameter. Measurements were made at two-week intervals, at approximately the same time of day, and by one of us.

## OBSERVATIONS

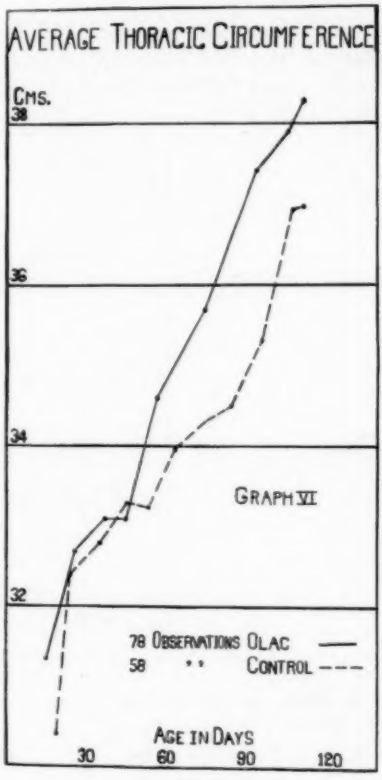
*Weights.*—The weights were taken before the 10 A.M. feeding on standardized beam scales. Individual weight records were grouped according to age and tabulated in ten-day periods (Graph IV). There was less than 1 gram difference in mean weight for the two groups at the beginning of the study. From the sixtieth day on, those infants fed the special mixture show a greater mean gain in weight than those of the control series. This difference increased until the completion of the problem.

*Heights.*—The measuring board used was that described by one of us previously (M. L. B.[2]). The average heights of the two groups tabulated in ten-day periods, are identical for the purposes of this problem (Graph V). There is 1 cm. difference in favor of the controls at the beginning of the problem, and less than 0.5 cm. at its conclusion.

*Circumference of the Chest.*—The measurements of the thoracic perimeter were taken at the mammary line, during the respiratory phase




Graph V

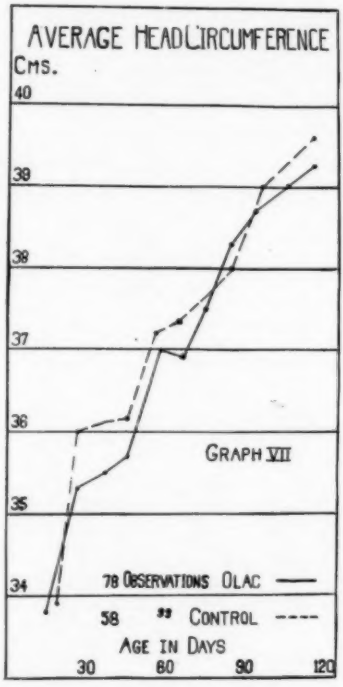



Graph VI

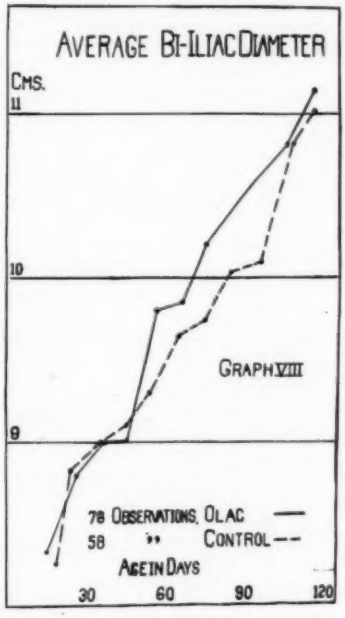
midway between inspiration and expiration. The arms were abducted from the body at 90 degree angles, and the forearms were above the head. The mean of three readings was recorded at each measurement, and tabulated at ten-day periods. Graph VI is a composite of these measurements. At the beginning of the study, both groups were nearly identical. From the forty-fifth until the one hundred and fifteenth day (the termination of the problem) the research group showed a greater thoracic circumference than did the controls.

*Circumference of the Head.*—There were no children in either group with clinical rickets, syphilis, microcephalus, or hydrocephalus. The average measurements of head circumference recorded at ten-day periods are shown on Graph VII. No significant differences were observed.

*Bi-iliac Diameter.*—This measurement, taken at the widest point of the iliac crest, was obtained with a sliding caliper. The composite result of this measurement is tabulated on Graph VIII. The differences between the two groups are insignificant.




Graph VII




Graph VIII

*Fat Absorption.*—Seven determinations were made of the total lipids and lipid partition of the feces (Table IV). Two babies were chosen at random from each of the two groups. Cod liver oil was eliminated from the diet for two weeks preceding each twenty-four-hour period of stool collection. Stools were collected on fat-free papers placed inside the diaper, so placed as to prevent an admixture of urine. Each stool, as soon as passed, was immediately placed in a refrigerator. The lipid determinations were made on the twenty-four-hour stool according to the method described by Holt.[3]

Seven twenty-four-hour stools were examined. Babies M. L. P. and R. H. were in the control series, and W. B. and A. S. were members of

TABLE IV

THE TOTAL LIPIDS AND THE LIPID PARTITION IN FECES

| NO. | AGE DAYS | WT. KG. | FAT* INTAKE % | CALC'D FAT GM./DA. | WET STOOL GM./DA. | DRIED STOOL | | | PARTITION GRAMS | | | S FECAL | | FAT PER CENT | | | FAT RETENTION | | CASE | DATE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | GM./DA. | FAT % | FAT GM./DA. | N. F. | UNSAP. | F. F. A. | SOAP | N. F. | UNSAP. | F. F. A. | SOAP | GM./DA. | % INTAKE RETAINED | | |
| 1 | 72 | 4.28 | 2.75 | 22.28 | 33.20 | 13.45 | 37.00 | 4.98 | 0.03 | 1.35 | 0.64 | 2.96 | 0.68 | 27.03 | 12.83 | 59.46 | 17.30 | 77.65 | M.L.P. | 6/29/36 |
| 2 | 74 | 4.33 | 2.75 | 22.28 | 42.70 | 17.30 | 26.75 | 4.63 | 0.12 | 0.87 | 0.31 | 3.33 | 2.58 | 18.69 | 6.73 | 71.96 | 17.65 | 79.21 | M.L.P. | 7/ 1/36 |
| 3 | 111 | 4.47 | 2.90 | 23.39 | 21.60 | 9.80 | 38.75 | 3.80 | 0.96 | 1.23 | 0.26 | 1.35 | 25.42 | 32.26 | 6.84 | 35.48 | 19.59 | 83.75 | R.H. | 7/ 1/36 |
| 4 | 113 | 4.09 | 2.90 | 23.39 | 30.00 | 15.20 | 37.50 | 5.70 | 0.17 | 1.14 | 0.21 | 4.18 | 3.07 | 20.00 | 3.60 | 73.33 | 17.69 | 75.63 | R.H. | 7/ 3/36 |
| 5 | 65 | 5.28 | 2.88 | 23.33 | 3.9 | 2.00 | 52.00 | 1.04 | 0.237 | 0.300 | 0.063 | 0.440 | 22.79 | 28.85 | 6.06 | 42.30 | 22.29 | 95.54 | W.B. | 7/ 3/36 |
| 6 | 55 | 4.16 | 2.88 | 23.33 | 13.70 | 5.75 | 77.50 | 4.46 | 0.65 | 1.58 | 0.65 | 1.58 | 14.65 | 35.48 | 14.39 | 35.48 | 18.87 | 80.88 | A.S. | 6/29/36 |
| 7 | 57 | 4.21 | 2.88 | 23.33 | 2.90 | 1.85 | 54.60 | 1.01 | 0.116 | 0.175 | 0.059 | 0.660 | 11.49 | 17.33 | 5.84 | 65.34 | 22.32 | 95.67 | A.S. | 7/ 1/36 |

*Calculated from the percentage of fat in undiluted evaporated milk and in olac dry powder.

Formulas for the above were as follows:

No. 1 and 2—
Evaporated milk ---------- 9½
Water ---------- 17½ } total 27 oz.
Dextrimaltose ---------- 4

No. 3 and 4—
Evaporated milk ---------- 10
Water ---------- 17 } total 27 oz.
Dextrimaltose ---------- 5

No. 5, 6, and 7—
Olac (27 calorie) ---------- 21 } total 27 oz.
Water ---------- 6

the problem group. The average percentage of fat retention by the babies fed olac was 90.69 per cent and that of the controls on evaporated milk, 79.06 per cent. This confirms Holt's conclusions that there is a higher retention of fat by infants fed olive oil than by those fed butter fat. The fat intake was calculated from the fat percentages given by the manufacturers of olac and of evaporated milk.

## CONCLUSIONS

1. A group of newborn and premature infants were fed formulas in which virgin olive oil was substituted for butter fat. The formulas were well taken and well tolerated.

2. The growth and development of the infants fed "olac" compared favorably with that of similar infants fed human or evaporated milk.

3. A study of the stool lipids confirmed the work of Holt, in which he demonstrated that the unsaturated long chain fatty acids, such as those found in olive oil, are better absorbed than the more saturated acids of cow's milk fat.

4. Olac has proved satisfactory as an initial food for premature infants, and its substitution in older premature infants presented no difficulties.

5. Olac is recommended as a complementary or substitute feeding for both normal and premature infants.

The authors wish to express their thanks and appreciation to Miss Cecelia Kortem, chief technician at St. Vincent's Infant and Maternity Hospital, for her aid in the lipid determination of the feces.

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# MULTIPLE FACIAL ANOMALIES

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FOR SOME years we have been interested in a syndrome of congenital facial anomalies which, in its totality, seems rare and sufficiently unrecognized to warrant recording. Incomplete representation of the factors that enter into the clinical picture is not so infrequent, but a fair search in the literature and inquiries among embryologists, anat-

Fig. 1.—J. M., six years old. Cleft palate, defective zygomatic arches, depressed lower lids with notch in the left one, deformity of both auricles, absence of opening into external auditory canal.

omists, and oral surgeons have yielded quite negative results both as to the occurrence and the pathogenesis of the full complex as shown in the five cases which form the basis of this report. An added interest lies in the fact that the occurrence of multiple facial anomalies, identical in nature and presumably in origin, in a series of children, will help to throw light on such isolated phenomena as microphthalmus or a deformed ear.

The clinical picture, here presented, includes the following features (Figs. 1, 2, 3, and 4. No convincing photograph could be obtained from one of the patients):

Fig. 2.—J. G. Cleft palate and cleft lip, defective zygomatic arch and microphthalmus on the left, deformity of both auricles with no opening into right, and small opening into left external auditory canal, preauricular tags.

Fig. 3.—M. M. Cleft palate, deficient zygomatic arches, bilateral depression of lower lids, deformity of both auricles. No opening into left external auditory canal.

1. Cleft palate or cleft lip, usually both. In this series of five children all of them had a cleft palate and four of them had also a cleft lip.

2. A defective zygomatic arch, as shown in a marked depression below the eye, both visible and palpable. This was bilateral in three and unilateral in two of the patients.

3. A sharp, angular notch, or downward depression, of one or both lower lids; or microphthalmus. Two of the children presented a bilateral, one a unilateral, deformity of the lids. Of the remaining two, one had an eyeball and cornea of about one-half the size of that of the normal eye, and the other had a rudiment of an eye that could be recognized as such only because of its site and the presence of a small pigmented area.

4. A deformity of one or both ears. In three patients both ears were affected; in a fourth, only one. The remaining child showed no obvious abnormalities. The deformities always involved the auricles. These were distorted and smaller than normal; some of them were mere nub-

Fig. 4.—J. K. Cleft palate and cleft lip, depressed zygomatic arch and sharply notched lower lid on right side. Mouth elongated to the right. Ears apparently normal.

bins. Three of the ears had no opening into the external auditory canal. One child had auricular tags in front of the ear. The hearing was defective in some of the children, apparently normal in others.

5. A tendency to mental retardation. Three of the children had intelligence quotients of 42, 54, and 85, respectively. One was apparently normal; the status of the remaining one was uncertain.

In addition to the above, some of the children showed absence of pneumatization of the mastoids at an age when one would expect it to be present.

As stated, combinations of several of these features are not infrequent. We have now under observation another baby with cleft palate and

cleft lip and microphthalmus with an eyeball and cornea of about one-half normal size. The frequency of this condition in association with the multiple congenital anomalies under discussion suggests a common etiology even when the microphthalmus occurs alone. This would seem to be substantiated further by the fact that the orbital cavity is said to be of normal size (Brüning and Schwalbe[1]). It is inviting to think that so striking a condition as microphthalmus has but one etiology.

Another child, fourteen months old, who was seen recently, presented another combination of facial anomalies such as we have never seen before and evidently belongs in our present category. The whole right side of the face was smaller than the left. There was the usual lack of development of the zygomatic arch, but the eyes were normal. The right auricle was distorted and was less than half the size of the left one. There was no opening into the external auditory canal. In front of and below the right ear and extending toward the mouth was a raised patch of auricular tissue about one inch long and from one-fourth to one-half inch in width. The slit of the mouth extended to the right at least one-half inch, so that both upper and lower lips, otherwise well formed, were on that side correspondingly that much longer than on the left side. Perhaps the most striking feature was a broad, rounded, shallow groove extending from the right angle of the mouth up to and below the right ear. The skin was normal, but all the underlying tissue, apparently including the maxilla, was involved. The outer part of this groove was the site of the misplaced auricular tissue. The nose deviated slightly to the right and was somewhat undeveloped on that side. The angle between the uvula and the soft palate on the left side was extended upward as a short slit.

It is beyond our purpose or ability to elucidate, much less attempt to add anything to, what is known about the embryologic sequence of events which brings these anomalies into being. An oral surgeon to whom we appealed for help and support wrote us among other things: "There are a number of variations occurring here which are not explained by embryologists, and until the latter can do better for us we are entitled to use a bit of imagination if only for our own amusement and to facilitate classification." In that spirit and with that object in mind we quote the following from Vilray Blair and Ralph B. Brown:[2]

"Congenital deformities of the mouth and face are most frequently related to some abnormality in the development or closure of the embryonal fissures, but there are many other types of deformities that do not have as definite a basis of origin.

"After the fifteenth day from conception the cavity from which will be formed the future mouth and nose is bounded above by a tubercle projecting from the anterior part of the head, called the frontonasal process, and on each side by the maxillary processes [Fig. 5]. The mandibular processes join in the midline about the fifth fetal week,

and they together form the lower jaw, which represents the first pair of visceral arches. The maxillary processes do not meet in the midline, but remain wedged between the frontal and the mandibular parts. The cavity is now bounded below by the mandible, laterally by the maxillary and above by the frontal processes. About this time there appear on the lower end of the developing frontal process three tubercles, which are in turn called the central and the two lateral processes. Each lateral tubercle is separated from the central by a short fissure called the lateral nasal groove, or olfactory pit. Farther on the lower border of the central processes are developed two other tubercles which are

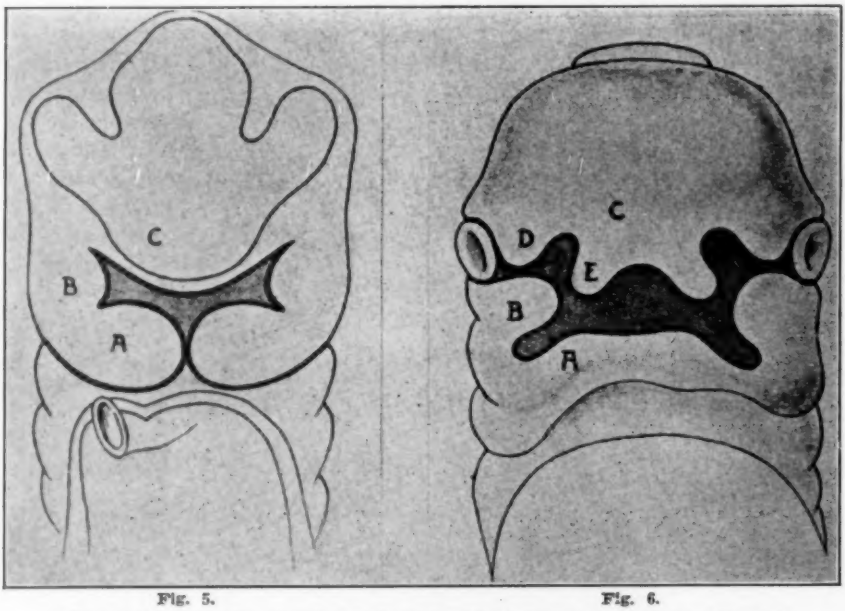


Fig. 5. Fig. 6.

Fig. 5.—Head of fetus at end of fifth week (after His). *A*, Mandibular processes; *B*, maxillary process; *C*, frontonasal process.

Fig. 6.—Head of fetus in the seventh week (after His). *A*, The now united mandibular processes; *B*, the maxillary process; *C*, frontonasal process; *D*, lateral nasal process; *E*, globular processes attached to the nasal part of the frontonasal process. The central nasal processes are separated from the lateral on each side by the lateral nasal grooves, which represent the anterior nares. From Blair and Brown: Practice of Pediatrics, W. F. Prior Company, Inc.

called the globular processes, and these are separated from each other by a single central groove. From the frontonasal process with the nasal processes will be formed the forehead, external nose and central part of the lip [Fig. 6].

"The maxillary processes are separated from the frontal, which now include the lateral nasal and globular processes, by the orbital fissure which extends to the mouth, in the upper part of which the eye is

developed. Somewhere below its middle the orbital fissure is joined by the lateral nasal groove, and together they have been described by Merkel as a *Y*-shaped cleft.

"The lower single limb of the *Y* opens into the mouth; while the external upper limb extends to the eye, and the upper median limb is the lateral nasal groove, which separates the lateral nasal from the central nasal process. The frontonasal and maxillary processes are separated from the lower jaw by a transverse fissure, the median part of which will be the future external mouth slit.

"By the nonclosure of any part of the *Y*-shaped fissures, the transverse mouth fissures, or the cleft that existed in the midline between the mandibular processes, or the medium groove between the globular

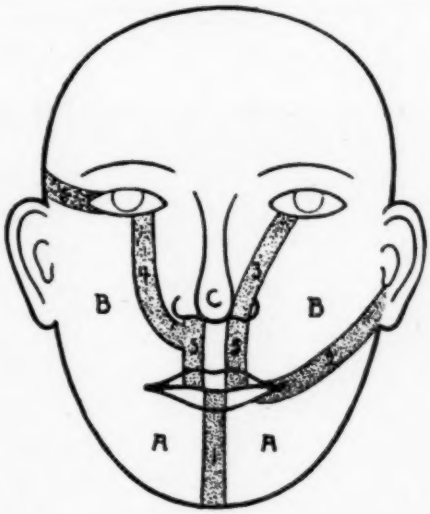


Fig. 7.—Schematic diagram, modified from Merkel, showing plan of facial clefts. From Blair and Brown: Practice of Pediatrics, W. F. Prior Company, Inc.

processes are produced any and all of the typical face clefts which are here schematically illustrated by a slightly modified diagram from Merkel [Fig. 7].

"A study of the regional embryology may give some idea of the variety and extent of defects that are possible, and, as in other areas of complicated development, one might decide that normal development is less to be expected than some deviation.

"Innumerable theories of the cause of deformities have been published, but in no single instance has any definite causative relation been established with any single deformity. All possible mechanical causes have been advocated; likewise injury, infection, malnutrition, tumors and maternal impressions. In some instances of the occurrence of extensive

deformities there may be such a striking injury, malnutrition, or nervous shock during pregnancy that it may be difficult to disassociate the occurrence from the deformity."

The text, figures, especially Fig. 3, and legends are at least interesting as to why, in a broad way, all of the lesions occur where they do, even if we must wait for the embryologists to give us further information as to the more precise developmental mechanism that brings them about.

The purpose of this report is to call attention both to a clinical complex of multiple congenital facial anomalies nearly identical in five instances, and to the probability that the isolated occurrence of a deformed ear, or microphthalmus, should be looked upon as a single manifestation of the same type and etiology as the other anomalies.

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# AN UNUSUAL CONGENITAL ANOMALY OF THE SPINE AND RIBS

## Extensive Spina Bifida Occulta, Probable Included Twin, and an Uncommon Fusion Anomaly of the Ribs

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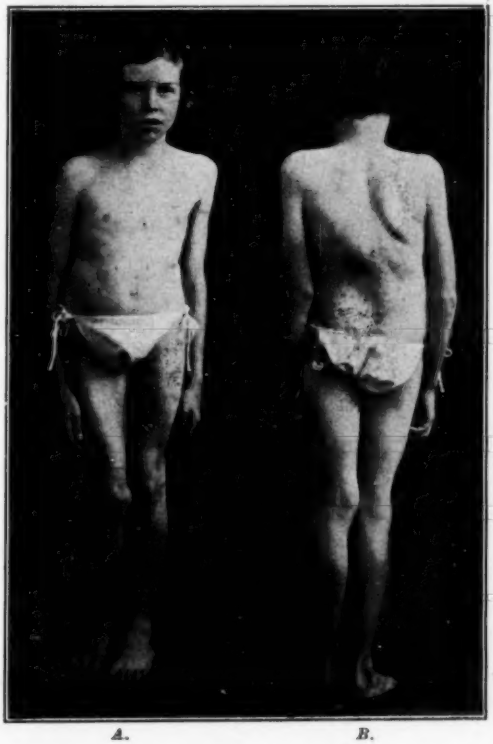
Marquette, Mich.

WHILE spina bifida occulta, even of marked degree, is a frequent observation, the following instance of lack of fusion of the spine, together with evidence of an aborted attempt at twinning, is of such remarkable character that its recording is worth while. The finding of an unusual rib fusion anomaly lends additional interest to this case.



*A.* *B.*

Fig. 1.—*A*, photograph taken August, 1934. Front view showing shortening and atrophy of right lower extremity with tilting of the pelvis. There is a prominence of the anterior chest wall on the left and some depression on the opposite side. *B*, back view showing dorsolumbar scoliosis with an associated moderate kyphosis.

From the Northern Michigan Children's Clinic, Marquette, Mich.

## CASE REPORT

M. H., a girl aged seven years, was first seen at the clinic in December, 1931. She was originally brought in for examination because of a limp and spinal curvature.

The patient, one of two children, was a child born at full term, whose family, feeding, and developmental histories, outside of the conditions to be presented, did not reveal anything of relevant significance. As far as could be determined, there were no congenital abnormalities in the immediate family and near relatives. The patient's past history was negative for any of the ordinary communicable diseases. In January, 1933, through an accident, she sustained a fracture of the right femur, which healed with malunion, necessitating an osteotomy later.

Fig. 2A.

Fig. 2.—*A*, taken Dec. 31, 1931. *B*, taken Aug. 8, 1936.
Roentgenograms of the spine and ribs showing almost complete lack of fusion of the vertebral column from the eighth thoracic vertebra down through the entire sacrum. Suggestive rudimentary rib extending from right segment of twelfth dorsal vertebra toward the opposite segment on the left. The bone corresponding to the third lumbar vertebra on the right has rudimentary lamellae, as do the lumbar vertebrae on the left. The two lowest lumbar vertebrae on the right appear to be hemivertebrae, whereas the corresponding bodies on the left are fused into one bony plate, both the hemivertebrae and bony plate having processes. The two lumbar columns are bridged by a bony structure. Note the anomalous fusion of the posterior ends of the tenth and eleventh ribs, bilaterally. The fusion of the ribs on the left is hidden behind the arched spinal anomaly and is not demonstrable in these roentgenograms.

According to the parents, the child gave evidence of a disturbance of sensation in the right leg early in childhood. However, she never showed evidence of appreciable weakness or paralysis of the extremities. A right-sided limp and a spinal deformity were noted soon after the child learned to walk.

Examination showed a scoliosis of moderate degree present to the left in the dorsolumbar region (Fig. 1). Below this a compensatory curvature to the right was noted. For a distance of approximately 3 inches between these curves, the spine was kyphotic, about 45 degrees to the horizontal. The right thigh showed a long, well-healed, surgical scar. The patient had a good range of motion at the right hip joint. There was 3 inches shortening of the right leg with an associated tilting of the pelvis. The chest was asymmetrical, a depression of the anterior chest wall on the right, and a prominence on the left being noted. Neurologic examination revealed a moderate degree of muscle atrophy of the right thigh and foreleg. There was no appreciable evidence of motor paralysis or sensory disturbance. The deep reflexes of the right lower extremity were considerably diminished. No pathologic reflexes could be elicited. The remainder of the examination did not reveal anything of significance.

Fig. 2*B*.—See legend on opposite page.

Roentgenologic studies were made of the entire spine, pelvis, and chest. Figure 2 represents roentgenograms taken at various visits to the clinic. The original films were submitted to Dr. Fred J. Hodges, head of the Department of Roentgenology, University of Michigan Hospital, for interpretation. His comments were as follows: "Although in this department we have had an opportunity of seeing numerous anomalies ranging from spina bifida occulta to multiple hemivertebrae, I am sure that the annals of this department include no such case as this. I think there is no question that an almost

complete lack of fusion of the two halves of the entire vertebral mass exists in the thoracic eighth to the twelfth, inclusive, and the entire group of lumbar vertebrae. In addition, there is a spina bifida occulta of fairly marked degree in the entire sacrum. One can see, also, anomalous fusion of the posterior ends of the tenth and eleventh ribs bilaterally. One can only speculate as to the situation of the spinal canal and the spinal cord."

Consideration of the roentgenologic findings reveals certain features that strongly suggest a developmental attempt at the formation of a double neural arch and lends support to the possibility of an aborted twinning process. Although the last dorsal vertebra appears to be represented by ununited left and right halves, the right member, fused to the vertebra above, seems to have a rudimentary rib extending toward the last dorsal vertebra on the left. Still considering the right side of the double column, one can observe that the bone which ordinarily would correspond to the third lumbar vertebra, has rudimentary lamellae. The same appears true of opposite bones of the left column. Farther down, the lower lumbar vertebral bones on the right appear to be hemivertebrae, while the corresponding bodies on the left are fused into one bony plate, both columns being bridged by a bony process at the lower end of the lumbar spine. It is noteworthy that the lumbar bodies composing this bony plate on the left have processes, as do also the corresponding hemivertebrae on the right.

Embryologically, several possible explanations are available as to the origin of the observed anomalies. It is to be remembered that in the blastemal stage of the embryo, the sclerotomes become differentiated into cephalic and caudal parts, the latter being the denser of the two. After this differentiation, each part grows mesially, fusing with its fellow of the opposite side, finally enclosing and obliterating parts of the notochord. The denser caudal portion then combines with the looser cephalic part to form the anlagen of the vertebrae. In the succeeding stage of development, the mesenchymal anlagen are converted into embryonic hyaline cartilage. Two centers of condrification now appear and soon fuse. It is conceivable that the anomaly of the spine could have had its inception in the blastemal stage by a failure of the opposing sclerotomes to grow mesially and fuse. On the other hand, the possibility presents itself that the spinal anomaly may, in fact, be an included twin. Whether, in regard to the origin of identical twins, one subscribes to the fission theory of Ahlfeld and others or to the fusion theory of Marchand and Ziegler, the abnormality here under consideration is amenable to explanation by either theory.

Although it is well recognized that a spina bifida occulta of fairly marked degree will often be accompanied by little or no clinical manifestations, it is surprising to find so few symptoms and clinical signs

in a defect of such extensive degree as appears roentgenologically in our patient. It is indeed a matter of great interest and speculation, as our roentgenologic consultant indicated, to conjecture as to the position of the spinal canal and cord.

While the unusual character of the vertebral abnormality is in itself remarkable, the fusion anomaly of the ribs is also worthy of note. In a review of the frequency and nature of congenital rib and spinal deformities, Meyer[1] and Shain[2] emphasize the relative infrequency of rib fusion anomalies below the fourth rib. It seems noteworthy, therefore, to recall that our patient revealed roentgenologic evidence of anomalous fusion of the posterior end of the tenth and eleventh ribs bilaterally. It is also interesting to note that Shain, in his personally observed case, likewise reports the occurrence of multiple rib fusion deformities associated with a spina bifida occulta of fairly marked degree, involving the cervicodorsal region and another involving the first sacral segment alone. The rib fusion anomalies in his case involved five ribs in the middorsal region on the left, three or more ribs in the upper dorsal, and two ribs in the middorsal regions on the opposite side.

## SUMMARY

A case of spina bifida occulta of extraordinary nature is recorded. The spinal defect is characterized by almost complete lack of fusion of the vertebral column, from the eighth thoracic vertebra down through the entire sacrum. Certain features are present in the roentgenologic picture that strongly suggest an aborted twinning process in the spine. The existence of a bilateral fusion anomaly of the ribs, involving the posterior ends of the tenth and eleventh ribs bilaterally, is an additionally uncommon finding.

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# ACTIVE SCURVY IN AN INFANT RECEIVING ORANGE JUICE

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THE literature on noncongenital scurvy contains very few case reports in which the condition was noted in children under four months of age. Alfred Hess[1] states that the earliest instance of scurvy which he has seen occurred in a baby four and a half months old. In the report of fifty cases of scurvy by McLean,[2] the youngest was three months old. In the group of 125 scorbutic cases reported by Park, Guild and Jackson,[3] the earliest case proved by clinical and x-ray studies was three months of age. A few authors[4] report even earlier cases of noncongenital scurvy.

In the following case report, I wish to emphasize three points: (1) the development of scurvy while the infant apparently received orange juice, (2) the age at which clinical signs of scurvy first developed, (3) the clinical and roentgenologic evidence of subperiosteal hemorrhage occurring after one month of intensive antiscorbutic therapy.

M. L. B. was admitted to the Henry Ford Hospital Oct. 29, 1936, at the age of three months eleven days with the chief complaint of swelling of the face and right leg. Family history: The mother's pregnancy was uneventful; her diet was adequate; she took little milk but large quantities of fresh fruit, bananas, apples, oranges, etc., every day, in addition to taking two capsules of a cod liver oil concentrate daily for the last five months of her pregnancy. Past history: Birth was a normal, spontaneous, full-term delivery. Birth weight was 6 pounds 10 ounces. The infant did not nurse well at the breast so she was put on a whole milk formula. Pasteurized vitamin D milk was used, and it was warmed but not boiled. At the age of two months, orange juice, 4 drams, and haliver oil with viosterol, 6 drops were given every day and the infant took both well. Present illness: The child seemingly did very well until Oct. 3, 1936, when, at the age of two and a half months, she appeared irritable, particularly when handled. A swelling was noted over the right maxilla, which progressed and eventually seemed to involve both sides of the face. Compresses to the affected area did not alter its course or relieve the infant's irritability. At the age of three months the child was even more irritable and cried when picked up or when her legs were moved. Within a few days it was noted that the right leg was swollen. This swelling increased in size and the child was brought to the hospital on Oct. 29, 1936. The infant's temperature was not taken during her illness at home, but the mother did not believe the child had much fever at any time. During her illness the child took her feedings well. Orange juice and haliver oil with viosterol were continued and she retained all food. Her stools were normal. No bleeding of the gums was noted. The infant was quiet except when disturbed.

Examination on admission showed a three-month, eleven-day-old female infant who appeared chronically ill, was very pale; irritable and cried when handled. Temperature was 100.4° F. (rectal); weight 11 pounds 9 ounces. There was no glandular enlargement. The head was of normal contour. The anterior fontanel measured 2

From the Department of Pediatrics, Henry Ford Hospital.

by 3 cm. and was flat; posterior fontanel was closed. No bossing or craniotabes was noted. The entire face appeared somewhat puffy, the cheeks appeared prominent but no masses could be felt. The submaxillary, submental and perotid glands were not enlarged to palpation. Both maxillae felt somewhat prominent and the infant cried and appeared to be in pain on palpation of these areas. No teeth were present; the gums were very pale in color. Flaring of the ribs and Harrison's groove were absent but the costochondral junctions were slightly prominent on palpation. The heart and lungs were normal. The abdomen was soft, liver was 2 cm. below the costal margin. There was slight bowing of both legs and there was a tender, indurated,

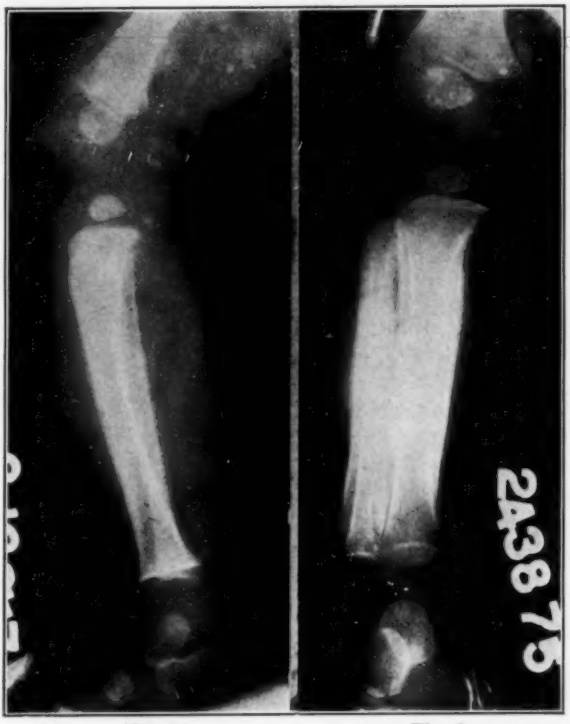


Fig. 1. Fig. 2.

Fig. 1.—Oct. 30, 1936. Note crevice and triangular area of decreased density at lower end of right femur.

Fig. 2.—Dec. 1, 1936. Calcification in subperiosteal hemorrhage in right tibia and fibula.

fusiform swelling over the middle of the right leg anteriorly with the skin over the central portion of the swelling discolored a bluish-brown. The infant definitely favored this extremity.

Laboratory Findings: Admission urinalysis showed four-plus white blood cells with an occasional clump; red blood cells, 3,250,000; hemoglobin, 8.40. Bleeding time was 5 minutes, clotting time 10 minutes; platelets, 240,000. Rumpel-Leede test was negative; Wassermann test, negative. Stool for occult blood negative.

Because of the severe secondary anemia she received three small transfusions within the first three days and three small transfusions during her subsequent stay

in the hospital. A urinalysis after the first three transfusions showed two-plus white blood cells, occasional red blood cell, rare hyaline casts, and two-plus albumin. Subsequent urine specimens showed occasional epithelial cells, rare white blood cells, no red blood cells, casts or albumin. Catheterized urine specimens were sterile.

Complete x-ray studies were made, and the first evidence of scurvy was noted in the right femur on Oct. 30, 1936, the day after admission. There was a crevice on the medial lower end of the femur with a triangular area of decreased density. The bones also had a ground-glass appearance. At this time x-ray plates of the right tibia and fibula failed to show any calcification in the subperiosteal hematoma. Subsequent x-ray examinations showed calcification of subperiosteal hemorrhage in all the long bones of the extremities with other typical scorbutic changes.

The child was placed on a whole boiled milk formula with 3 ounces of orange juice and 15 drops of viosterol. She took and retained all of the orange juice and viosterol but refused part of her formula for several weeks.

There was a marked decrease in the size of the swelling of the right leg in four days, and the discolored central skin area disappeared. However, the infant remained irritable when handled and the temperature ranged from 99° to 101° F. (rectal) with an occasional rise as high as 102° F.; cebione therapy, 25 mg. daily, was started on Nov. 24, 1936. On Nov. 30, 1936, one month after admission, a very large tender fusiform swelling appeared in the left forearm and the infant refused to move the arm. Because of evidence of continued active scurvy as demonstrated by the swelling and tenderness of the left forearm and irritability when disturbed, cevitamic acid, 30 mg. three times a day, was given intravenously for three days. Following this improvement was very rapid. The child's irritability decreased to such an extent that she could be picked up without crying; the temperature subsided to normal; and the swelling of the left forearm gradually decreased in size. Subsequent x-ray plates showed calcification in the subperiosteal hemorrhage in the left radius and ulna.

On discharge, Dec. 14, 1936, the child appeared healthy, took her diet well and was gaining weight. Two teeth erupted during her stay in the hospital without any bleeding from the gums, although during the first few weeks the gums were quite hyperemic. The swelling of the face completely disappeared.

No roentgenograms were taken of the malar bones until one month after admission, and these plates were not diagnostic. Whether the malar swelling, which was the first sign noted in the child's illness, was due to subperiosteal hemorrhage or merely the edema which sometimes accompanies scurvy, we are unable to state. The urinary findings are somewhat confusing. The report of four-plus white blood cells with occasional clumps was obtained from a casual specimen. Subsequent clean specimens contained only an occasional white blood cell. The

two-plus albumin and red blood cell in the urine after the three transfusions might be directly related to the transfusions, or due to the child's scorbutic state. An irregular fever is usually found in scurvy and in this case was undoubtedly due to the child's scorbutic state.

In view of the fact that this child received large doses of vitamin C by mouth in the form of orange juice for one month and as cebione for six days prior to the development of clinical signs of subperiosteal hemorrhage in the left radius and ulna, I am inclined to credit the mother's statement that she gave the infant 4 drams of orange juice every day starting at the age of two months.

We can only speculate why scurvy should remain active in an infant receiving large doses of vitamin C and why, in the first place, the child should ever have developed scurvy. The fact that three days of intravenous medication with vitamin C cleared up all signs of active scurvy would point to temporary faulty absorption by the gastrointestinal tract, notwithstanding the fact that the infant took and retained all her medication and had normal bowel movements.

Since discharge from the hospital the child has received from 2 to 3 ounces of orange juice every day and has shown no further evidence of scurvy.

## SUMMARY

1. Scurvy developed in an infant who apparently received 4 drams of orange juice every day.

2. Clinical symptoms of scurvy were first noted at the age of two and a half months.

3. Scurvy remained active notwithstanding large doses of vitamin C per oram, until vitamin C was given intravenously.

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# THE VARIABILITY OF THE KAHN REACTION IN CHILDREN

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THE specificity of serologic tests for syphilis is not indisputable. Until such time as the mechanism of the reaction and the various factors concerning it are clearly understood, it must be regarded in the same light as other laboratory procedures in arriving at a clinical diagnosis. This attitude becomes justifiable when one finds fluctuations in the serologic reactions in presumably healthy children of normal healthy adults. To stigmatize these children as syphilitic purely on a single positive serology would be doing them and their progenies a grave injustice.

This report concerns twelve apparently nonsyphilitic children, seen in the past two years, whose Kahn tests on the blood were positive on one or more occasions. Such cases are not common since during this period of time (July, 1934, to April, 1936) approximately 6,500 new cases were seen in the pediatric clinic, each of which had a routine standard Kahn test on the blood. The incidence was therefore close to 1 to 550. However, the rarity of such cases does not minimize their importance. The salient features of the twelve cases are summarized in Table I. In this group there were seven girls and five boys. In no instance was there a family history which could be considered even suggestive of syphilis. Four gave weak Kahn reactions which in all but one instance became negative, and the remainder gave strong Kahn reactions which in due time became negative. It is noted in the protocol that infection, either acute or chronic, was present in eleven of the cases. One (Case 7) was free from infection, but in four of the children (Cases 3, 9, 10, and 12) febrile periods were associated with a positive serology. In two (Cases 3 and 10) there seemed to be no relation between the degree of fever and the Kahn reaction. In Case 9 the Kahn reaction became negative when the fever subsided. In Case 12 the Kahn test on the spinal fluid remained positive, but only by the presumptive method, which is considered more sensitive than the standard test and is not relied upon for a positive diagnosis. In one child pathologic examination of the tonsils revealed chronic infection such as is seen in syphilis and the Levaditi silver staining method demonstrated the presence of spirochetes which morphologically resembled the *Spirochaeta pallida*. Nevertheless, this child's physical examination was essentially normal; blood Kahn tests on the parents

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TABLE I

BLOOD KAHN REACTIONS

| CASE | NAME | HOSP. NO. | AGE | CLINICAL DIAGNOSIS | DATE | REACTION | COMMENT |
|---|---|---|---|---|---|---|---|
| 1 | D. O. ♀ | 367852 | 13 yr. | Acute upper resp. infect. Septic tonsils. Chronic otitis media supp. with mastoiditis (rt.). | 8/29/35<br>9/26/35 | ++<br>Neg. | Afebrile.<br>No clinical evidence of syphilis. |
| 2 | C. L. ♂ | 360624 | 8 yr. | Bronchopneumonia (unresolved). | 5/23/35<br>5/24/35<br>6/30/35<br>8/28/35<br>3/21/36 | ++++<br>++++<br>Neg.<br>Neg.<br>Neg. | Afebrile. No clinical evidence of syphilis. Kahn test on spinal fluid (6/28/35) negative. Colloidal gold negative. Received 4 intramuscular injections of bismuth salicylate gr. i from 6/13/35 to 7/3/35 at weekly intervals. |
| 3 | O. E. B. ♂ | 359186 | 6 yr. | Pneumonitis. Acute catarrhal otitis media. | 5/ 2/35<br>5/ 3/35<br>5/ 8/35<br>5/11/35<br>5/15/35<br>5/16/35 | ++++<br>++++<br>+++<br>++<br>±<br>Neg. | 105° F. (r) No clinical evidence of syph-<br>100° F. (r) ilis. Serology on parents<br>99.5 F. (r) negative.<br>100° F. (r)<br>100° F. (r)<br>100° F. (r) |
| 4 | B. H. ♀ | 361563 | 11 yr. | Septic tonsils and adenoids. | 6/ 6/35<br>6/ 7/35<br>6/ 8/35<br>3/26/36 | ++<br>++<br>±<br>Neg. | Afebrile. No clinical evidence of syphilis. Blood Kahn test on parents and siblings negative. Pathologic study of tonsils with silver stain revealed spirochetes morphologically like *Spirochaeta pallida.* |
| 5 | J. B. ♂ | 368183 | 9 yr. | Septic tonsils and adenoids. Upper respiratory infection. | 9/ 4/35<br>9/ 9/35<br>10/ 7/35<br>10/23/35 | ++++<br>++++<br>Neg.<br>Neg. | Afebrile throughout. No clinical evidence of syphilis. Blood Kahn test on mother negative. |
| 6 | V. H. ♀ | 372591 | 2 yr. | Acute suppurative otitis media and mastoiditis. Varicella (12/12/35). | 11/15/35<br>11/18/35<br>12/10/35<br>12/21/35 | +<br>++<br>+++<br>+ | Afebrile. No clinical signs of syphilis. Blood Kahn test on parents negative. Organisms isolated from middle ear—*Str. hemolyticus, Staph. aureus,* and *Hemophilus influenzae.* |

TABLE I—CONT'D

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 7 | S. F.<br>♀ | 359403 | 7 yr. | Error of refraction. | 5/ 6/35<br>5/ 8/35<br>5/10/35 | +++<br>±<br>Neg. | Afebrile at all times. No clinical evidence of syphilis. |
| 8 | R. M.<br>♂ | 367120 | 13 yr. | Septic tonsils. Osteochondritis (vertebrae). | 8/20/35<br>8/21/35<br>8/26/35<br>8/30/35<br>9/26/35<br>1/ 2/36 | ++++<br>++++<br>++<br>+<br>Neg.<br>Neg. | Tonsils and adenoids removed 9/28/35. No evidence of syphilis clinically. Afebrile throughout. |
| 9 | E. Z.<br>♀ | 376964 | 6 yr. | Pneumonitis. Atelectasis. *Ascaris lumbricoides.* | 2/23/36<br>2/24/36<br>2/27/36<br>3/10/36 | ++++<br>+++<br>++<br>Neg. | 104° F. No clinical signs of syphilis. Blood 100° F. Kahn test on parents negative. 101° F.<br>Normal. |
| 10 | H. S.<br>♀ | 372646 | 21 mo. | Ruptured appendix. Peritonitis. Death. | 11/17/35<br>11/22/35 | ++++<br>Neg. | 102°-104° F. W.B.C. 31,000<br>102° F. W.B.C. 15,200<br>No clinical evidence of syphilis. Necropsy showed no syphilitic lesions. Blood Kahn test on parents negative. |
| 11 | M. C.<br>♀ | 339412 | 13 yr. | Hemolytic jaundice. Myocarditis. Pericardial effusion? Bacterial endocarditis. | 7/ 5/34<br>7/ 6/34<br>7/ 9/34<br>7/20/34<br>8/20/34<br>3/ 5/36<br>3/11/36<br>4/15/36 | +++<br>++<br>+++<br>++++<br>++++<br>Neg.<br>Neg.<br>Neg. | Kahn tests repeatedly negative at the Children's Clinic of the University of Michigan at Marquette, Mich., during the past 2 years. Blood Kahn test on parents negative. Presents no stigmas of syphilis. Temperature normal at time of the Kahn tests. Received 8 injections of bismuth salicylate gr. i intramuscularly from 7/14/34 to 9/7/34. No other treatment. |
| 12 | E. J.<br>♂ | 373968 | 19 mo. | Influenza, pneumonia, and meningitis. Death. | 12/14/35<br><br><br><br>12/17/35 | Spinal fluid ++<br>Presumptive positive<br><br><br>Neg. (Spinal fluid)<br>Presumptive positive | Blood Kahn negative. Colloidal gold 00000011221, mastic 344443, globulin ++++, cells 4,000 per c.mm. Temperature 101°-104° F.<br>Colloidal gold 0001224421, mastic 445543, globulin ++++, cells 9,000 per c.mm. Temperature 101°-104° F. No evidence of syphilis at autopsy. |

and siblings were negative, and the serology on this patient became negative. It seems very unlikely that the child had syphilis. The organisms mistaken for *Spirochaeta pallida* were in all probability Spirilli of Vincent. Two other patients giving positive serology tests died, but no evidence of syphilis was found at autopsy or on subsequent tissue examination. A few antisyphilitic injections were given in Cases 2 and 11, but we think their effect was of no significance. Case 11 is of interest because Kahn tests performed elsewhere were persistently negative while those done in our serologic laboratory were positive five times then became negative and have remained so. No explanation is offered for this lack of agreement. Exception may be taken to Case 6 in that a negative serology was not obtained, but the existence of syphilitic infection is highly improbable, and it is quite likely that if further blood tests were made they would have been negative.

What is the reason for a positive serology? Lipoproteolytic ferment is known to be present in abundance in the serum of syphilitics. This is due to the rich lipoid content of the *Spirochaeta pallida*. Because of this it has been suggested that the Wassermann and the Kahn tests are merely a means of determining the amount of lipoproteolytic ferment present in the serum. This enzyme substance, it is thought, is produced mainly by lymphocytes and plasma cells, and it is stimulated to production by the lipoids. While this may be true, Kahn[2] strongly feels that other factors, biologic and physicochemical, as yet unidentified, play a significant rôle in the development of positive serology. These factors, though most frequently found in syphilis, may be present in other diseases or abnormal functional states. This being so, a positive serology should not be considered as absolutely pathognomonic of syphilis. Other corroborative evidence is necessary.

False positive serology is not common. A recent survey made by the United States Department of Public Health[3] indicates that any of the serodiagnostic tests now used to detect syphilitic infection may give a false reaction. Leprosy, tuberculosis, malignant neoplasms, artificial or natural fever, menstruation, malaria, jaundice, and pregnancy are listed as causes of positive serology in the absence of syphilis. Of particular significance is the fact that in this investigation the Kahn standard diagnostic test gave the smallest number of false serologic reactions. It did not yield positive reactions in malignant neoplastic diseases, in fever, pregnancy, or menstruation, and for the rest of the above mentioned group the incidence of false serology was only 0.2 per cent. None of the normal nonsyphilitic cases investigated (152) gave a positive serology. As far as can be ascertained from the record of these competitive studies, the bloods for the serologic tests were obtained almost entirely from adults. In view of our findings such data are extremely interesting. With the exception of one

case, positive reactions in our group were associated with infection. In the absence of infection no determining factor could be demonstrated. Fever may have accounted for the positive serology in two instances (Cases 9 and 12). In a previous report[4] from this clinic, no false positive reactions were found in the many febrile conditions listed, but one false positive reaction was recorded in a boy, aged eight years, with Sydenham's chorea; in another child with septic tonsils and adenoids the presumptive Kahn test was positive.

We do not know how long a temporary positive serology may last. In our series, one (Case 11) remained positive for at least six weeks. The child was sent home and did not return for over a year, at which time the Kahn test was negative. Frequent Kahn tests were not done to determine when the reaction became negative in the other cases.

It seems that infection was a primary cause of the false serology in the patients recorded in this report. The possibility of technical errors in carrying out the tests cannot be entirely overlooked, but this is very unlikely in view of the highly trained personnel under the direction of Dr. Kahn. It would be worth while to follow the blood of a positive reactor over a long period of time, and particularly if possible through several illnesses, in order to determine if the same or similar factors are responsible for a return of a positive serology. It may be that other serodiagnostic tests for syphilis would not have given false readings, but this is improbable in view of the low incidence of false serologic reactions obtained by the Kahn (standard) test as compared with those by other methods.

## CONCLUSIONS

The main purpose of this communication is to emphasize strongly that a positive serology does not always mean that syphilitic infection is present. This fact is clearly demonstrated by eleven cases in our series in which the Kahn reactions were positive at first but later became negative. Only two of these patients received antisyphilitic therapy, a few injections of bismuth salicylate being given which would ordinarily be insufficient to change the serologic reaction. There were no clinical stigmas of syphilis in any of the cases, nor could positive family histories of infection be elicited. When the blood of the parents was available, it gave negative serologic reactions.

Our plea is against a hasty diagnosis of syphilis based on a positive serology with no other evidence to support the diagnosis. If there is no clinical evidence of syphilis and the family history is negative, repeated serologic tests should be made. In our opinion "false positive" reactions may persist for several weeks or longer, and the test should be repeated at frequent intervals before antisyphilitic therapy is instituted. Once treatment is begun, it may be difficult to determine accurately the child's status should the serology subsequently become

negative. It is our belief, and we present the 12 cases in the protocol as our proof, that a fluctuating serology which becomes less markedly positive and finally negative without intensive antisyphilitic therapy to explain it is not indicative of syphilis.

## SUMMARY

Infants and children suffering from acute or chronic infection with or without fever may in isolated instances give temporary positive serologic reactions. Serologic tests should therefore be repeated for a sufficiently long period of time to eliminate the possibility of fluctuating type of reactions.

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# UNTREATED SERONEGATIVE MOTHERS OF SYPHILITIC CHILDREN

## Report of Two Cases

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ONLY two untreated seronegative mothers of children with prenatal syphilis were admitted to the United States Public Health Service Venereal Disease Clinic, Hot Springs, Ark., during the seven years 1930 to 1936, inclusive. Blood serum Wassermann reactions, spinal fluid examinations, and careful physical examinations revealed no evidence of syphilis in these two mothers.

There is no doubt but that the two children of the two seronegative mothers had prenatal syphilis, rather than acquired syphilis, as both children had bilateral interstitial keratitis, hutchinsonian upper central incisors, saddle noses, and four-plus blood serum Wassermann reactions.

### CASE REPORTS

Case 1.—L. M. D., white, female, aged thirty-seven years, married a second time, was admitted from Newport, Ark., June 10, 1936. She felt well in every respect and came to the clinic merely to accompany her daughter, G. M.

*Family History.*—Her first husband had been treated for syphilis one year before marriage. The first child, born in 1919, had a four-plus Wassermann reaction and a skin eruption shortly after birth. He received some treatment for syphilis but died at the age of one year.

A second child, K. M., female, aged sixteen years, married, was admitted to the clinic Aug. 19, 1936. Her blood Wassermann reaction had been four-plus a short time after her birth and she had received antisyphilitic treatment, resulting in a negative Wassermann reaction at that time. Her physical examination and her Kolmer and Kahn tests were negative on Aug. 19 and Aug. 20, 1936.

The third child, G. M., female, aged fourteen years, single, was admitted June 10, 1936, complaining of sore eyes for the past six months. Her Wassermann reaction had been four-plus at the age of five, at which time she received oral medication only. She had no complaints at that time. Her Wassermann reaction was also four-plus at the age of six years, and she received 5 doses of neoarsphenamine. She felt well at that time. Her first trouble began with her eyes. The right eye became sore (photophobia) in January, 1936. The left eye became similarly involved about one month before admission. She received 8 doses of neoarsphenamine from January, 1936, to May 10, 1936.

Examination on admission showed a well-nourished, ambulatory, stocky, white girl, 5 feet 2 inches tall, weighing 110 pounds. She had a saddle nose and notching of the upper central incisors (hutchinsonian). There was an interstitial keratitis and iritis of both eyes, i.e., bilateral photophobia, much more marked in left eye;

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marked circumcorneal injection of left eye, slight injection of right eye; haziness of both corneas. Hymen was intact. Nothing else was noteworthy. Blood pressure was 96/70 and the urine was negative. Kolmer and Kahn tests were four-plus, June 10 and 11, 1936, July 27, 1936, Aug. 24, 1936, and Sept. 21, 1936.

*Diagnosis.*—Late prenatal syphilis.

*Course.*—Photophobia decreased twenty-four hours after the first dose of arsphenamine. Photophobia and circumcorneal injection disappeared entirely within three weeks after treatment with arsphenamine and bismuth was instituted. Haziness of the corneas was diminished.

*Past History.*—The mother stated that she had had at least twenty negative blood Wassermann tests from the birth of the first child in 1919 to 1933, and that she had never had a positive Wassermann test. She denied any genital lesions and treatment for syphilis. She had had five miscarriages, i.e., in 1921-23-30-31-32.

Physical examination of the mother on admission showed a well-nourished, ambulatory, white female, not ill. The examination was negative in every respect including the eyegrounds. Blood pressure was 132/94.

*Laboratory Findings.*—Urine was negative. Blood serum Kolmer and Kahn tests were negative on June 10 and 11, 1936, and Aug. 5, 1936. On June 17, 1936, spinal fluid tests showed Kolmer negative, cells 3, globulin negative, mastic 00000.

*Diagnosis.*—No evidence of syphilis at present (spontaneously cured).

CASE 2.—R. L. B., colored female, married, aged forty-eight years, was admitted from Jonesboro, Ark., July 11, 1936. She felt well in every respect and came to the clinic merely to accompany her daughter, T. B.

*Family History.*—The husband and seven children, aged twelve to thirty-one, were at home but there was no history obtainable. One child, T. B., female, aged fourteen years, single, was admitted to the clinic July 11, 1936, complaining of a swelling of the right knee and a sore on the right leg of about two months' duration; a foul nasal discharge for one year; and haziness of both corneas, which began about six years previously. She had never had a Wassermann test or treatment for syphilis.

Examination on admission showed an ambulatory, limping, under-sized, slender, colored child, 4 feet 2 inches tall, and weighing 57 pounds. There was bilateral haziness of the corneas (interstitial keratitis), a saddle nose with foul-smelling mucopurulent discharge at the anterior nares (gummatous osteitis with necrosis of the nasal bones), and notching of the upper central incisors (hutchinsonian). There was also swelling with limited motion of the right knee and only moderate pain, and a sinus of the mesial surface of the right knee just below the knee joint. Hymen was intact and blood pressure was 80/60.

Anterior, posterior, and lateral radiographs were made of the right knee including the lower third of the femur and upper half of the tibia and fibula. In the femur about 2 inches above the epiphyseal line and in the anterior cortical portion there was an area of rarefaction about 2 cm. in circumference. A similar area was found in the anterior portion of the tibial cortex about 2 inches below the epiphyseal line. There was no evidence of any periosteal proliferation. The cortex of the tibia posteriorly had the striated appearance often seen in congenital syphilis. The areas of rarefaction were reported as probably those of a gummatous osteitis.

*Laboratory Findings.*—The urine was negative. Blood serum Wassermann (Kahn and Kolmer) tests were four-plus on July 11, 13, and 21, 1936, Aug. 31, 1936, and Sept. 24, 1936.

*Diagnosis.*—Late prenatal syphilis.

*Course.*—Swelling of the knee and leg disappeared, and the sinus of the leg healed within one month after arsphenamine and bismuth treatment was instituted. The discharge from the nose was greatly improved. The corneas were unimproved.

*Past History.*—The mother denied genital lesions and treatment for syphilis. She had had no previous Wassermann tests. There had been two miscarriages, 1923 and 1931.

Physical examination of the mother on admission showed a well-nourished, ambulatory, colored female, not ill. The entire examination, including the eyegrounds, was negative.

*Laboratory Findings.*—The urine was negative. Blood serum Wassermann (Kolmer and Kahn) tests were negative on July 11, 13, 15, 16, 1936, Aug. 14, 1936, Sept. 14, 1936, and Oct. 2 and 8, 1936, some of them after provocative arsphenamine. On Sept. 10, 1936, spinal fluid findings were as follows: Kolmer test negative, cells 2, globulin trace, mastic 00000.

*Diagnosis.*—No evidence of syphilis at present (spontaneously cured).

During the seven-year period from 1930 to 1936, inclusive, there were 78 mothers of 89 syphilitic children admitted to the Hot Springs Clinic (Table I).

TABLE I

SUMMARY OF MOTHERS OF SYPHILITIC CHILDREN

| SERONEGATIVE ON ADMISSION | | | | TOTAL | | SEROPOSITIVE ON ADMISSION | | GRAND TOTAL | |
|---|---|---|---|---|---|---|---|---|---|
| NO PREVIOUS TREATMENT | | SEROPOSITIVE BEFORE TREATMENT INSTITUTED PREVIOUS TO ADMISSION | | | | | | | |
| NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| 2 | 2.6 | 6 | 7.7 | 8 | 10.3 | 70 | 89.7 | 78 | 100.00 |

Although only 70 (89.7 per cent) of our mothers were seropositive on admission, a total of 76 (97.4 per cent) were seropositive on admission or had had a four-plus blood Wassermann reaction before treatment had been instituted previous to admission (Table II).

TABLE II

| UNTREATED PATIENTS SERONEGATIVE ON ADMISSION | | SEROPOSITIVE ON ADMISSION OR SEROPOSITIVE BEFORE TREATMENT INSTITUTED PREVIOUS TO ADMISSION | | TOTAL | |
|---|---|---|---|---|---|
| NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| 2 | 2.6 | 76 | 97.4 | 78 | 100.0 |

Stokes[1] states: "The mothers of our series yielded an equal proportion of positive blood Wassermann reactions (50 per cent); but later studies such as those of Jeans and Cooke found in younger material than ours, 85 per cent, and Wile in earlier material from the standpoint of age of infection, 95 per cent positive bloods. . . . At best, in our study, we were obliged to rate 21 per cent of the mothers of syphilitic children as negative to an ordinary clinical and serological examination."

The following table is from Stokes' *Modern Clinical Syphilology*, second edition (Table III).

TABLE III

WASSERMANN REACTION IN MOTHERS OF SYPHILITIC CHILDREN

| AUTHOR | YEAR | CASES | TYPE | WASSERMANN | |
|---|---|---|---|---|---|
| | | | | POSITIVE (%) | NEGATIVE (%) |
| Jeans[2] | 1916 | 73 | ---------- | 85.9 | |
| Solomon, Hand[3] | 1922 | 33 | ---------- | 80 | 4 |
| White and Veeder[4] | 1922 | 151 | 44 per cent of the children under two years of age | 84 | 6 |
| Strandberg[5] | 1922 | --- | ---------- | 87 | |
| Stokes[6] | 1924 | 139 | 11 per cent of the children under two years of age | 60 | |

A review of this literature does not reveal, except in Wile's series, whether or not the seronegatve mothers had ever been treated for syphilis or had been seropositive previously. It is stated that 95 per cent of Wile's 100 mothers had positive Wassermann reactions, that they were chiefly early cases, and all were untreated. Although, as previously stated, only 89.7 per cent of our mothers were seropositive on admission, 7.7 per cent who were seronegative on admission gave a definite history of a four-plus blood Wassermann reaction before treatment had been instituted previous to admission, thus making a total of 97.4 per cent known to have had a four-plus Wassermann reaction, and only 2.6 per cent who were seronegative and had received no previous treatment. Therefore, Wile's series of 5 per cent seronegative mothers is the most nearly comparable to ours with 2.6 per cent.

Stokes[1] states: "The proportion of positive blood Wassermann reactions obtained in the mothers of syphilitic children will vary with the age of the mother and the child who is under investigation. The young mothers of syphilitic infants produce the highest proportion of positives because of the activity and short duration of their infections."

The ages of the mothers in our series were as shown in Table IV.

TABLE IV

| AGE | WHITE | COLORED | WHITE AND COLORED | |
|---|---|---|---|---|
| | NO. | NO. | NO. | PER CENT |
| 16-20 | 9 | 3 | 12 | 15.4 |
| 21-25 | 18 | 5 | 23 | 29.5 |
| 26-30 | 13 | 6 | 19 | 24.4 |
| 31-35 | 9 | 3 | 12 | 15.4 |
| 36-40 | 4 | 1 | 5 | 6.4 |
| 41-45 | 4 | | 4 | 5.1 |
| 46-48 | 2 | 1 | 3 | 3.8 |
| | 59 | 19 | 78 | 100.0 |

Our mothers were young for the greater part, 44.9 per cent of them being from sixteen to twenty-five years of age, and 69.3 per cent of them from sixteen to thirty years of age. The ages of the children in our series are shown in Table V.

TABLE V

| AGE (YEARS) | WHITE NO. | COLORED NO. | WHITE AND COLORED NO. | WHITE AND COLORED PER CENT |
|---|---|---|---|---|
| Less than 1 | 11 | 1 | 12 | 13.5 |
| 1 to 2 | 5 | 4 | 9 | 10.1 |
| Total 2 yr. or less | 16 | 5 | 21 | 23.6 |
| 2 | 6 | | 6 | 6.7 |
| 3 | 4 | | 4 | 4.5 |
| Total 3 yr. or less | 26 | 5 | 31 | 34.8 |
| 4 | 5 | 2 | 7 | 7.9 |
| 5 | 5 | 3 | 8 | 9.0 |
| Total 5 yr. or less | 36 | 10 | 46 | 51.7 |
| 6 to 10 | 19 | 6 | 25 | 28.1 |
| 11 to 15 | 9 | 7 | 16 | 18.0 |
| 16 to 20 | 2 | | 2 | 2.2 |
| Grand total | 67 | 22 | 89 | 100.0 |

There were 23.6 per cent of the children in our series who were less than two years of age, 34.8 per cent less than four years of age, and 51.7 per cent of them who were five years old or less. In White and Veeder's series, 44 per cent of the children were less than two years of age, and in Stokes' series, 11 per cent. The oldest child in our series was nineteen years old.

The spontaneous cure of syphilis without treatment has been noted —Bruusgaard's analysis of Boeck's series,[7] Stokes and Des Brisay.[8]

If it should be assumed that the two mothers in our series never had syphilis, it would be contrary to the present generally accepted notion of the maternal transmission of syphilis by the diaplacental route rather than the paternal transmission (Stokes[1]).

Colles[9] in 1837 stated that the child of a syphilitic father will render its mother immune against syphilis: "A newborn child affected with congenital syphilis, although it may have symptoms in the mouth, never causes ulceration of the breast which it sucks, if it be the mother who suckles it, although continuing capable of infecting a strange nurse."

Fournier,[10] Diday,[11] and Ricord,[12] and Hutchinson[13] in his later years held the view of Colles although in earlier years Hutchinson[14] had believed that it was "possible for the poison to pass over in a mode very different, indeed, from that of chancre-contagion and, therefore, not unlikely to be followed by very different results." The

reason for the mother being apparently immune to syphilis is that she already has syphilis. Moore[15] states, "For all practical purposes, Colles' law may be dismissed as invalid; the paternal transmission of infection, the mother being healthy, does not exist; and the child in utero cannot be infected unless the mother herself has syphilis."

There is a difference of opinion as to whether the benign clinical and serologic course of syphilis in women is due to pregnancy.

Swediaur[16] noted in 1809 that syphilis is likely to run a rather benign clinical course in women. In 1810 Bertin[17] considered at least a part of the benign clinical course of syphilis in women to be due to pregnancy.

Brown and Pearce[18] in 1920 studied experimentally the factor of pregnancy in producing latency or regression of syphilis, but in 1924[19] they found that this was not absolutely conclusive.

Chesney[20] found that the behavior of pregnant and nonpregnant female rabbits to syphilitic infection was about the same.

Moore[15] states, "If a woman acquires syphilis just before, coincident with, or shortly after impregnation the usual manifestations of early syphilis are often completely suppressed, or if present, are milder in degree than in nonpregnant women or in men. This beneficial effect of pregnancy on syphilis is not limited to the early stages of the infection, but often extends throughout the lifetime of the patient and affords a considerable degree of protection against the appearance of late lesions, especially neurosyphilis. . . . a properly controlled pregnancy may be a valuable therapeutic measure in the treatment of syphilis in women, enhancing the probability of an ultimately favorable outcome."

Moore's studies[21, 22] as to the beneficial effect of pregnancy upon the course of syphilis have been noted not to be free from criticism by Ingraham and Kahler[23]: "For example, even though in the outpatient department, it was possible for Moore to show that latency was almost twice as common in women as in men (24 per cent as compared with 47.5 per cent), of the 1,085 women with Wassermann positive latent syphilis 470 (43.3 per cent) were pregnant at the time of the first observation—Turner.[24] The incidence of latency, and indeed of symptomless or almost symptomless syphilis in the population at large, is very difficult to determine—Fordyce,[25] and most of these women would have remained undiscovered had not a routine of Wassermann reaction on all pregnant patients been done. The incidence of latency among males might be found to be nearly as great, did pregnancy attract as much attention in their behalf. On the other hand, both clinically and pathologically, Wile[26] and Warthin,[27] latent syphilitic women seem extraordinarily free from many elective signs of syphilitic disease in heart and blood vessels, as well as in the parenchyma of the cord and brain, Moore,[21, 22] Solomon,[28] Bilote,[29] as

compared with men, Abraham,[30] Hemsath,[31] Pillsbury,[32] Roberts.[33] That pregnancy is the biologic agent causing this picture is not yet demonstrated.

"In all probability the effect of pregnancy on the syphilitic infection in the gravid woman is, in most instances, not sufficient to make any appreciable difference from the purely diagnostic standpoint."

However, the Cooperative Clinical Group[34] found: "Syphilitic women who had had adequate antisyphilitic treatment (at least 20 injections of an arsenical and 20 injections of a heavy metal) showed clinical progression or relapse of their syphilis in only 4 per cent of the cases if they were pregnant since the infection. The altered metabolic processes of pregnancy appear to change the course of syphilis favorably since the percentage rose to 7 where no pregnancy intervened during or after treatment of the mother's syphilis. Among the group who received inadequate treatment and who were pregnant after the infection, clinical progression or relapse was noted twice as often as in the adequately treated group. For the colored woman pregnancy seems to be an even better auxiliary treatment for syphilis than it is for the white woman. The pregnant woman had a smaller percentage of the infectious type of relapse than the nonpregnant woman. In the group with early syphilis the apparent protection of pregnancy is well indicated by the absence of a single case of early central nervous system relapse when adequate treatment was given, whereas in the nonpregnant group one-half of the clinical progressions or relapses were an involvement of the central nervous system. Pregnancy apparently plays no rôle in the ultimate outcome; if anything, it undermines the resistance of the patient to the syphilitic infection after the disease has reached the late stage.

"Clinical progression or relapse was noted in a fifth more of adequately treated cases not pregnant during or after treatment for their syphilis than in the group pregnant during or after treatment. Among the adequately treated cases pregnant since infection, the colored women had 6 per cent more of satisfactory results than the white women."

Stokes[1] states, "Speaking from a statistically unevaluated experience, I should feel no hesitancy in subscribing to Moore's views on the marked effect of pregnancy (when it occurs at the time of, or subsequent to, infection) in reducing the severity of syphilis in the woman."

Kemp and Menninger's study[35] "suggests that while pregnancy may alter the course of early syphilis, it is not the only factor responsible for the decreased incidence of neurosyphilis in females in contrast to males. On the contrary, it suggests that the incidence of neurosyphilis may be increased in women in whom impregnation coincides with or occurs within a short time after infection. It appears also that pregnancy does not influence the incidence of neurosyphilis when it occurs after invasion of the neuraxis is established."

It would appear, therefore, from a review of the above mentioned literature that there is no difference of opinion as to the benign clinical course of syphilis in women, but there is a difference of opinion as to whether pregnancy is the cause of this.

## SUMMARY

There are presented two cases of untreated seronegative mothers of children with prenatal syphilis. Among 78 mothers of children with prenatal syphilis admitted to this clinic during the seven years 1930 to 1936, inclusive, only 2 (2.6 per cent) were seronegative on admission or gave no history of a previous positive Wassermann reaction. Six (7.7 per cent) mothers who were seronegative on admission had been seropositive before treatment had been instituted previous to admission.

Although only 70 (89.7 per cent) mothers were seropositive on admission, a total of 76 (97.4 per cent) were seropositive on admission or had been seropositive before treatment had been instituted previous to admission. The nearest comparison to our series is Wile's series of 95 per cent seropositive mothers of syphilitic children.

Of the mothers in our series, 44.9 per cent were from sixteen to twenty-five years of age, and 69.3 per cent were from sixteen to thirty years of age. Of the syphilitic children in our series, 23.6 per cent were less than two years of age, 34.8 per cent less than four years of age, and 51.7 per cent less than five years of age.

Whether or not pregnancy had anything to do with the apparently spontaneous cure of syphilis in the two mothers of our series cannot be determined. A review of the literature shows that there is no difference of opinion as to the benign clinical course of syphilis in women; but there is a difference of opinion as to whether pregnancy is the cause of this.

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# FEVER THERAPY IN CHILDREN

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ALTHOUGH therapeutic hot baths have been used for centuries, treatment with high fever started only in 1918, when von Jauregg[1] reported the benefit of malaria on general paresis. Observations of the effect of fever on growth, virulence, and specificity of organisms, potency of toxins, immunologic factors, and chronic diseases have stimulated fever therapy studies.

The various methods of producing fever, many of which have been discarded, are listed below.[2] Their effect probably is due to the heat produced rather than to the method.

I. Inoculation with infectious diseases
   A. Malaria, tertian
   B. Recurrent (relapsing) fever
   C. Sodoku (ratbite fever)

II. Injection of avirulent bacteria and their products
   A. Tuberculin
   B. Typhoid vaccine (T.A.B.)[3, 4, 5] and its fractions ("H" antigen)[6]
   C. Gonococcus vaccine
   D. *Hemophilus ducreyi* vaccine (dmelcos)
   E. Saprophytic vaccine (neosaprovitan B.)
   F. Streptococcus vaccine
   G. Mixed autogenous vaccine
   H. Pyrifer (German bacterial preparation, *Streptococcus erysipelatis* and *Bacillus prodigiosus*)

III. Injection of nonspecific chemical and biologic products
   A. Sodium nucleinate
   B. Milk
   C. Peptone
   D. Turpentine
   E. Sulphur
   F. Blood (autohemotherapy)
   G. Other nonspecific proteins

IV. Oral drugs
   A. Phenylethylhydantoin (nirvanol)

V. Physical measures
   A. Hot baths
   B. Multiple electric pads and heating blankets

From the Department of Pediatrics, Duke University School of Medicine, and Duke Hospital.

C. Diathermy[7, 8]
D. Radiothermy[9]
E. Radiant energy (infra-red)[10, 11]
F. Air-conditioned cabinets (Kettering hypertherm)[12, 13]
G. Inductotherm[14]

These last five physical agents have the great advantage of accurate temperature control and consequent greater safety for the patient. Though the apparatus is more costly than the inoculation material used for fever therapy, the net expense is less, as a shorter period of hospitalization is required. A comparison of various electrical methods for producing fever indicates that the radiant energy method is the most convenient and economical, and that the clinical results are equal to those obtained by other methods.[10]

## RISKS OF FEVER THERAPY

Twenty-nine deaths have occurred among 4,809 treated patients, a mortality of 0.6 per cent.[15] All deaths have occurred within three days after treatment. Sudden death has occurred in several instances, apparently due to circulatory collapse. Pathologic studies of dogs and two adults revealed congestion of all the organs, degeneration of liver cells, hemorrhagic encephalitis, hemorrhagic pneumonia, and cortical degeneration and hemorrhage of the adrenals.[16] A postmortem examination of a child of twelve years showed similar changes.[17] Herpes of the cornea, cerebral hemorrhage, tetany, and convulsions are the nonfatal complications.

## PHYSIOLOGIC REACTIONS TO FEVER[13, 18]

The pulse rate may increase 18 beats for each degree centigrade elevation (10 beats for each degree Fahrenheit). The blood pressure rises at first but later falls; the pulse pressure frequently remains high due to lowered diastolic pressure. The cardiac output shows an increased minute volume output, and the blood flow may increase more than fourfold. The blood volume, viscosity, red blood cell count, and hemoglobin remain unchanged, if blood concentration is prevented. The leucocyte count,[19a] after a variable early reduction of both lymphocytes and neutrophiles, may increase to three times the initial figure, mainly due to an increase in young neutrophiles. Counts at twenty-minute intervals show fluctuations of 30,000 in cell level until the peak is reached. The lymphocytes and monocytes decrease in number early in the treatment but later (nine to eighteen hours) there is an increase due to the appearance of new cells. Hemograms are almost identical during short and long periods of high fever. Splenic contraction, excitement, convulsions, cyanosis, and absence of the spleen do not affect the hemograms.

The blood sugar, calcium, and plasma lipid concentrations are unchanged. The urea nitrogen, urea, uric acid, and creatinine may be slightly increased, probably due to blood concentration. The inorganic phosphorus decreases and is converted to the organic form. The oxygen content and capacity of venous blood are increased. Serum proteins remain the same or are slightly and transiently increased. The increase in lactic acid may cause the $CO_2$ combining power to fall as low as 35 volumes per cent. Hyperventilation may then result in alkalosis with a blood pH as high as 7.6. The blood plasma chloride decreases 50 to 75 mg. per cent and children lose a total of 10 to 15 grams. The sweat may contain as much as 5.87 grams of chloride (expressed as NaCl) per liter.[19b] Secretion of free hydrochloric acid in the stomach practically ceases and urinary chloride content decreases. The urine is scant, highly colored, has a high specific gravity, and may become slightly alkaline. Increased nitrogen elimination through the perspiration results in a decrease in the rate of urinary nitrogen excretion. The metabolic rate usually increases about 12.5 per cent for each degree of fever (centigrade) rise (7 per cent per degree Fahrenheit) regardless of the fever method used.[20] Electrocardiograms show a decrease in amplitude of deflection of the QRS complex. In dogs the increased creatinine clearance is in direct proportion to the height of the temperature.[21]

## IMMUNOLOGIC REACTIONS TO FEVER

The complement fixing bodies in rabbits immunized against staphylococcus, streptococcus, *Micrococcus catarrhalis* and diphtheroid bacilli become temporarily reduced; a similar reduction occurs in the serum of patients with gonorrhea. Studies on agglutinins in man are contradictory. The agglutinins for typhoid organisms in rabbits are reduced and may be completely lost after repeated heatings. No change occurs in the opsonic index.

## METHOD

Complete details of the radiant energy cabinet which we used are published elsewhere.[10, 11] We are indebted to Dr. Stafford L. Warren for advice in its construction. It consists of a cellotex-lined box which fits over the bed and encloses the reclining patient completely except for the head (Figs. 1 and 2). Radiant energy is furnished by seven 120-watt carbon filament bulbs which are connected with a series of switches so that any number may burn at one time. The temperature is taken with an ordinary rectal thermometer, or with an electrical thermometer which is kept constantly in the rectum.

The patient is given 10 to 15 grams of sodium chloride in capsules during the twenty-four hours preceding the treatment. He is given an enema, a liquid breakfast, and sedatives (codeine or bromides) one-half hour before being placed in the cabinet, which has been warmed to 40° C.

(104° F.). His body is covered with towels to prevent possible burns and an ice bag is placed on his head; an electric fan blowing on the head increases the patient's comfort. The rectal temperature reaches the desired level in one and one-half or two hours. The temperature of the

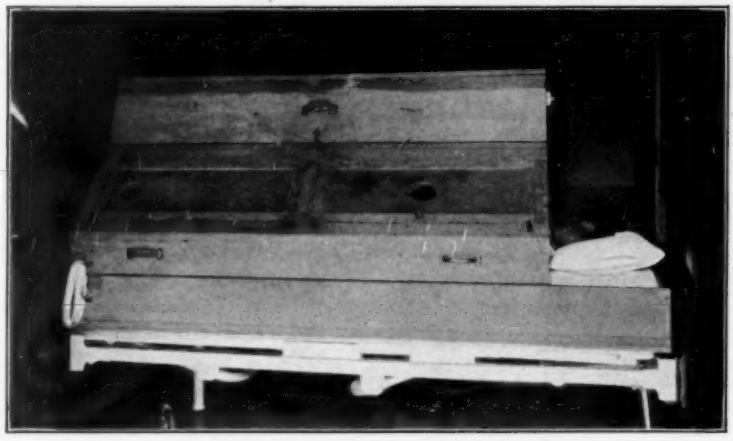

Fig. 1.

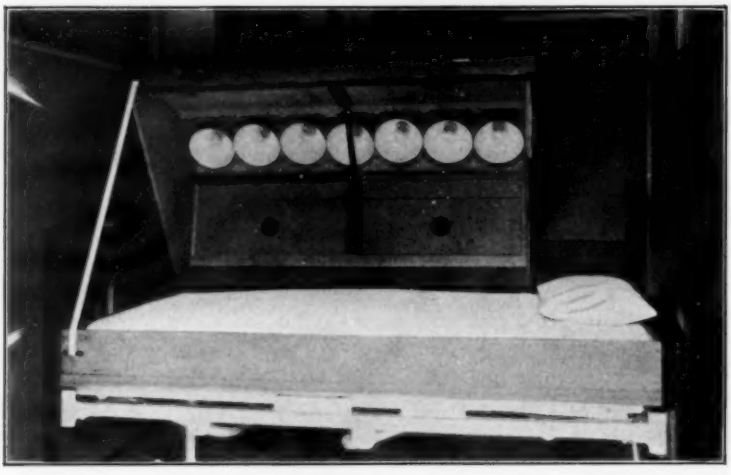

Fig. 2.

Figs. 1 and 2.—Photographs showing radiant energy cabinet used for fever therapy in children.

cabinet usually reaches 50° to 55° C. (122° to 131° F.), but after the patient's maximal temperature is reached, a box temperature of 40° to 41° C. will maintain the desired level. As the temperature rises, the patient usually becomes restless, perspires profusely, and may complain

of heat, headache, abdominal pain, nausea, or other sensations. The skin becomes red except for pallor about the mouth. After the temperature reaches 40° C. (104° F.), he becomes relatively comfortable and drowsy, sleeping most of the time, but occasionally requesting water. Sedatives may be necessary. Two thousand to 4,000 c.c. of liquids and 10 to 15 grams of sodium chloride in capsules, or as 0.6 per cent solution, are given during the treatment. The temperature, pulse, and respiration are recorded every ten minutes and the blood pressure every half-hour (Chart 1). After the treatment, the patient is removed from the cabinet and given a tepid sponge. By these measures, the temperature will reach normal in an hour. For a more rapid reduction, sponging with

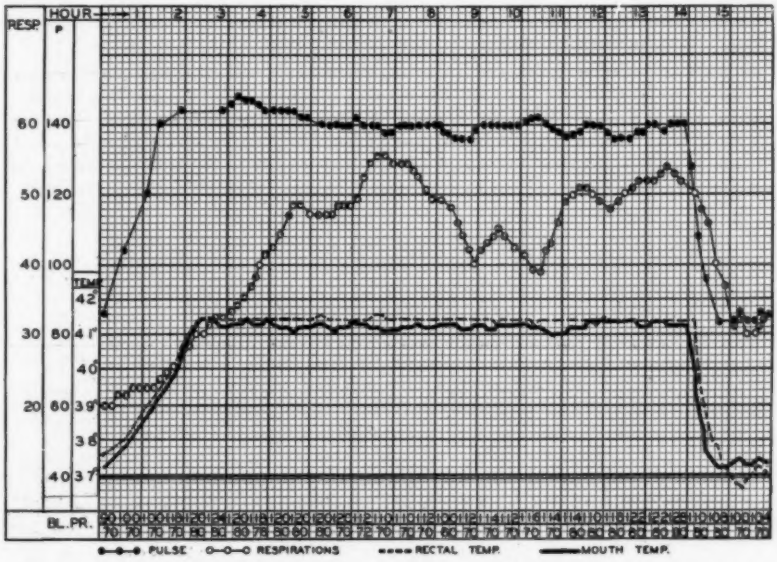


Chart 1.—Typical record of temperature, pulse, respiration, and blood pressure in a child treated at 41.5° C. for twelve hours.

alcohol and an electric fan are of value. The physiologic reactions at 41.5° C. and 40.5° C. are similar.

Abdominal distention and pain, and vomiting occur in 50 per cent of the treatments. Occasionally there may be mild headache and delirium. Some patients may have localized muscle tremors of the extremities or convulsions, which probably are due to alkalosis resulting from hyperpnea; these may be stopped by allowing the patient to breathe 5 per cent carbon dioxide in oxygen or by the intravenous injection of calcium gluconate. Fever therapy should be discontinued when convulsions occur. As a rule patients have maintained or gained weight during heating. It should be emphasized that fever therapy

should be used only in hospitals in which the patient is under constant medical and nursing supervision.

Artificial fever has been used in treating the following diseases: Syphilis, gonorrhea, chronic infectious arthritis, chorea, multiple sclerosis, asthma, inflammatory lesions of the eye, rheumatic fever, pneumonia, mycosis fungoides, circulatory disturbances of extremities, epilepsy, scleroderma, bronchiectasis, lung abscess, tumors, psychosis, subacute bacterial endocarditis, staphylococcus septicemia, chronic osteomyelitis, encephalitis, tuberculosis, trichiniasis, meningitis (streptococcic), leucemia, brucellosis, poliomyelitis, Parkinson's syndrome, noma, and rabies. The various pediatric conditions for which fever therapy has been given at Duke Hospital are tabulated in Table I.

TABLE I

CHILDREN TREATED AT DUKE HOSPITAL

| NUMBER OF PATIENTS TREATED | NUMBER OF TREATMENTS | NUMBER OF FEVER HOURS |
|---|---|---|
| 32 | 70 | 460 |

| DISEASES TREATED | NUMBER OF CASES |
|---|---|
| Gonorrheal infections* | 8 |
| Chronic infectious arthritis | 7 |
| Syphilis† | 4 |
| Chorea | 8 |
| Encephalitis | 1 |
| Hodgkin's disease | 1 |
| Tuberculous meningitis | 1 |
| Undulant fever | 1 |
| Leucemia | 1 |

*The gonorrheal cases include ophthalmia (3), vaginitis (5), epididymitis (1), arthritis (2).

†The syphilitic cases include one of interstitial keratitis.

GONORRHEAL INFECTIONS

*Neisseria gonorrheae* is easily affected by heat, for example urethritis may subside during a febrile illness, and the organism is killed at 41.5° C. (106.7° F.) in six to twenty-seven hours[19c, 22] (Table II). Gonorrheal infection may be treated at 41.5° C. for five hours, although if the patient is tolerating the treatment well, it should be continued for eight to twelve hours, so that cure may result from one treatment. Varia-

TABLE II

THERMAL DEATH TIME OF 15 STRAINS OF GONOCOCCI IN VITRO
(Carpenter, Boak, Mucci, and Warren)

| TEMPERATURE (DEGREES C.) | PER CENT KILLED | DEATH |
|---|---|---|
| 39 | Some injurious effect on growth of organisms | |
| 40 | 99.7 in 10 hr. | In 8 strains death of all the cells not obtained at 30 hr. |
| 41 | 99 in 4-5 hr. | 11-23 hr. |
| 41.5-42 | 99 in 2 hr. | |
| 41.5 | 100 | 7-20 hr. |

tions of the thermal death time of different strains explain the lack of uniformity of the results of fever therapy. Eighty to ninety-five per cent of patients obtain clinical and bacteriologic cures when sufficient fever treatment is given.[23, 24, 25, 26]

*Gonorrheal vaginitis in children* is amenable to fever therapy from hot water baths, radiant energy cabinets, or vaginal diathermy[23, 27] (Table III).

TABLE III

THE RESULTS OBTAINED WITH DIATHERMY IN GONOCOCCUS VAGINITIS (Crossen)[27]

| | | |
|---|---|---|
| Number of weeks till first negative smear | (acute) 10 cases<br>(chronic) 5 cases | (Average)<br>16.2 wk.<br>4.2 wk. |
| Number of weeks till consistently negative smear | (acute) 10 cases<br>(chronic) 5 cases | 21.6<br>4.6 |
| Average time followed after consistently negative smear | (acute) 10 cases<br>(chronic) 4 cases* | 12½ mo.<br>33½ mo. |

*One followed for only three months after consistently negative smear.

*Gonorrheal arthritis* if treated early and adequately by fever therapy is cured in 80 per cent of the patients and markedly relieved in an additional 10 per cent.[7, 13, 23, 24, 25, 28] By maintaining a temperature of 41.5° C. for ten to twelve hours even better results may be obtained.

In *gonorrheal ophthalmia*[24, 29] the swelling and discharge decrease rapidly during the first few hours of fever treatment so that irrigating fluids can reach the infected area. One or two treatments usually cure the patient and prolonged hospitalization and nursing care are not required (Table IV).

CHRONIC INFECTIOUS ARTHRITIS[13, 25, 30]

The immediate results of fever therapy at 40 to 40.5° C. (104 to 105° F.) sometimes are dramatic. The results probably are due to an improvement of the circulation to the joints. An increase in pulse volume,[31] and in size and number of the capillaries of the finger[32] has been observed during fever. The pain usually diminishes or disappears, increased mobility of the joints results, and frequently the swelling and redness subside. Patients who have been incapacitated for months because of pain, swelling, and limitation of motion have returned to work after one or two treatments. The final results depend more upon the duration and severity of the disease, and the after-care, than on the number of fever treatments. It has been estimated that 10 per cent of the patients treated for chronic infectious arthritis are free from symptoms; 25 per cent obtain marked relief; 35 per cent, moderate relief and 30 per cent, no relief.[13] Table V summarizes our cases of infectious arthritis. The average age of the patients was ten and three-tenths years; the youngest was seven years and the oldest fourteen. The average duration of the disease before fever therapy was twelve and nine-

TABLE IV

ANALYSIS OF CASES OF GONORRHEAL INFECTIONS

| CASE NO. RACE, SEX, AGE (YR.) | DIAGNOSIS AND CONDITION ON ADMISSION TO DUKE HOSPITAL | RESULTS OF FIRST TREATMENT AT 41.5° C. FOR 12 HR. | RESULTS OF SECOND TREATMENT AT 41.5° C. FOR 8 TO 12 HR. | DAYS OF HOSPITALIZATION |
|---|---|---|---|---|
| 61294<br>C., ♀, 7 | Ophthalmia lasting 8 days. Positive smears. Profuse discharge from eyes and corneal ulcer.<br>Vaginitis. Profuse discharge. | Discharge and swelling absent. Smears still positive.<br>Discharge scanty, smears positive. | Discharge absent and smears consistently negative. Ulcer healing.<br>Discharge absent and smear negative. No follow-up. | 11 |
| 51562<br>C., ♂, 6 | Ophthalmia lasting 4 days. Profuse discharge, redness, and swelling of left eye. Smears positive. | Discharge and swelling slight. Smears negative. | Treated because of infection of right eye, which cleared. Smears persistently negative. Well for 5 mo. | 14 |
| 64199<br>C., ♂, 6 | Ophthalmia lasting 8 days. Profuse discharge, redness and swelling of both eyes. Prolapse of right iris and corneal ulcer of left eye. | Discharge and swelling slight. Smears positive. | Discharge and swelling absent. Smears positive, becoming negative one week later. Right eye lost. Corneal ulcer of left eye healed. Hospitalized 2 wk. for healing right eye. No follow-up. | 20 |
| 60201<br>W., ♀, 10 | Vaginitis lasting one year. No improvement with sitz baths. Profuse vaginal discharge present. | Discharge absent. Persistently negative smears. | Second treatment not required. Well 4 wk. later. | 10 |
| 47373<br>C., ♀, 13 | Vaginitis lasting 5 wk. Profuse discharge.<br>Arthritis lasting 4 wk. Pain and swelling of toe and wrist and soreness of shoulder. | Treatment for 3 hr. Diminution of discharge. Smears still positive.<br>Marked immediate improvement in pain, swelling, and tenderness. | Second treatment not given. No follow-up. | 3 |
| 33055<br>C., ♀, 2 | Vaginitis lasting 3 wk. Profuse discharge. No improvement with sitz baths. | Treatment terminated after 5 hr. because of convulsions. Discharge continued. | Treatment terminated after one hour because of convulsions. Discharge continued and smears remained positive. Insufficient treatment. Condition cleared after 4 to 5 mo. | 9 |
| 46332<br>C., ♀, 3 | Vaginitis lasting 2 wk. Profuse discharge.<br>Arthritis lasting 5 days. Pain and swelling of ankle. Congenital syphilis. (See Table VIII.) | After one 8-hr. treatment the discharge stopped. Smears became persistently negative and the arthritis subsided. | Similar treatment given. Followed for 17 mo. | 13 |
| 54635<br>C., ♂, 15 | Urethritis and prostatis lasting 4 wk. Profuse discharge. Arthritis lasting 12 days. Pain in shoulders, knees, ankles, toes. Fever. | Disappearance of genitourinary symptoms and marked improvement in the arthritis. | Second treatment not given. Gonococci found in prostatic smear 2 wk. later. Patient symptomless 2 mo. after treatment. | 19 |

TABLE V

ANALYSIS OF CASES OF CHRONIC INFECTIOUS ARTHRITIS TREATED WITH FEVER

| CASE NO. RACE, SEX, AGE (YR.) | CONDITION ON ADMISSION TO DUKE HOSPITAL | CONDITION AFTER TREATMENT AT 40.5° C. FOR 5 HR. | RESULT |
|---|---|---|---|
| 27360 W., ♂, 12 | Duration 16 mo. Bedridden for 8 mo. Pain, swelling, and deformities of all joints. | Pain much less. Swelling diminished. Mobility greater and limbs easily manipulated. Five treatments given. | On discharge, patient was walking with a cane. Recurrence of symptoms 8 mo. later. No marked improvement after 2 treatments. One and one-half yr. later patient was bedridden. |
| 29499 W., ♀, 14 | Duration 6 mo. T & A no benefit. Unable to walk. Pain, swelling, and limitations of motion of elbow, wrists, and ankle. | Pain much less; swelling diminished. Mobility increased. Two treatments given. Walked after first treatment. | On discharge, patient walked without pain. Recurrence of symptoms 4 mo. later. Further treatments unsuccessful because of lack of cooperation. Unimproved 1 yr. later. |
| 29556 W., ♂, 7 | Duration 2 yr. General glandular enlargement, enlargement of spleen, fever. Pain decreased mobility of wrists, spine, jaw. Swelling in wrists and ankles. | Marked decrease in pain and mobility and slight reduction of swelling. Three treatments given. Fever unchanged. | Recurrence of symptoms 2 mo. later with improvement after one treatment. Recurrence 7 mo. later and improved only in pain after treatment. Disease progressing one year later. |
| 20529 W., ♀, 11 | Duration 3 mo. No improvement after T & A and vaccines. Pain, swelling, and limitation of motion of all joints of extremities. | Pain and mobility greatly improved after one treatment. Swelling affected to a less extent. | Improvement had continued when patient was seen 9 mo. later. |
| 23768 W., ♀, 11 | Duration 20 mo. Marked pain, swelling, and limitation of motion of joints of extremities. | Pain and swelling less. Slight increase in mobility after 2 treatments. | Five mo. later, pain was very slight. Swelling and limitation of motion unchanged. |
| 38282 W., ♀, 8 | Duration 9 mo. Tenderness and swelling of ankles. No limitation of motion. | Slight improvement in pain and swelling after 2 treatments. | Patient not seen since discharged from hospital. |
| 31920 C., ♂, 9 | Duration one yr. Disease quiescent. Slight swelling of all joints of extremities and limitation of flexion of fingers. | Slight decrease of swelling and increased mobility of fingers. Two treatments given. | Patient not seen since discharge from hospital. |

tenths months (three to twenty-four months). One to seven fever treatments were given to each patient (average two and seven-tenths hours). Pain was mainly affected by fever therapy, and swelling to a less extent. The improvement in mobility depends more upon the relief of pain than upon decrease in the size of the joints. The skin temperature about the affected joints is grossly higher for days after the fever. The immediate results are worth while, but the late results are disappointing. After discharge from the hospital, return visits were infrequent because of the distances the patients had to travel; no treatment was given at home. We believe that fever therapy is a valuable adjunct in the treatment of chronic infectious arthritis but should not be used to the exclusion of medical, physiotherapeutic, and orthopedic measures.

TABLE VI

THERMAL DEATH TIME OF *Treponema pallidum* IN VITRO
(Boak, Carpenter, and Warren)[35]

| TEMPERATURE (DEGREES C.) | NUMBER OF HR. NECESSARY TO RENDER INFECTIVE EXTRACTS INNOCUOUS TO OTHER RABBITS |
|---|---|
| 39.0 | 5 |
| 40.0 | 3 |
| 41.0 | 2 |
| 41.5 | 1 |

## SYPHILIS[33, 34]

The *Treponema pallidum* is destroyed at 41.5° to 42° C. in one hour in vitro[35] (Table VI), in six hours in vivo (rabbits),[36] and in two hours if the lesion itself is raised to 40° C.[37] Physical methods of fever therapy produce results in paresis comparable to those obtained by malarial treatment. The difficulty in producing high fever by the injection of typhoid vaccine has been overcome by giving a second injection at the height of the fever produced by the first.[38] The use of "H" antigen has been advocated for patients who are unable to undergo the severe reaction of whole typhoid vaccine.[6] In neurosyphilis, many observers have found fever therapy combined with or followed by chemotherapy to be more effective than fever alone. The Wassermann test became negative in four of seven Wassermann-fast syphilities.[33] The results obtained in asymptomatic neurosyphilis are especially good. In early syphilis the chancre responds rapidly to fever therapy alone but the serology is unchanged and recurrences of the chancre may occur.[39] Failure of cure of syphilis in the primary stage may be due to the fact that the skin temperature is 1° C. lower than that of the rectum. Fever therapy is beneficial in congenital syphilis though the results are not as good as those in the acquired type. Table VII gives a summary of the results of various treatment methods.

In *interstitial keratitis* favorable results have been obtained by injecting foreign proteins. Malarial therapy has been shown to be of value

and often will improve cases resistant to the usual antisyphilitic measures.[40] Good results also are obtained with the use of fever produced mechanically.[19d, 41]

A summary of our treated syphilitic patients is given in Table VIII. The serology of patients 1 and 3 was not changed by fever which probably was insufficient. The period of observation was too short. The serology of patient 2, constantly under antisyphilitic therapy, became negative one and one-half years later; the paretic child showed definite improvement after the second series of arsphenamine and fever therapy. The rapid change of the spinal fluid to normal is noteworthy. In patient 5, with interstitial keratitis, two treatments caused disappearance of much of the exudate in the anterior chambers and of the corneal opacities. Six months later, the patient, having received no specific therapy in the interim, could barely distinguish large objects. Antisyphilitic therapy following the fever probably would have maintained the improvement.

TABLE VII

SUMMARY OF RESULTS OF TREATMENT IN JUVENILE PARESIS (Menninger)[34]

| | TOTAL CASES | MARKED IMPROVEMENT | SLIGHT IMPROVEMENT | NO CHANGE | WORSE | DIED |
|---|---|---|---|---|---|---|
| Malaria | 67 | 8 | 20 | 33 | 2 | 4 |
| Arsphenamine | 35 | 1 | 2 | 15 | 12 | 5 |
| Tryparsamide | 22 | 3 | 10 | 4 | 1 | 4 |
| Tryparsamide and malaria | 12 | 2 | 3 | 5 | 2 | 0 |
| Diathermy | 8 | 6 | 1 | 1 | 0 | 0 |
| Total | 144 | 20 | 36 | 58 | 17 | 13 |

## CHOREA[3, 4, 17, 19d, 42]

Temperature of 40 to 41° C. (104 to 106° F.) produced by phenylethylhydantoin (nirvanol), injections of typhoid and paratyphoid vaccines and physical methods has been of inestimable value in the treatment of chorea. Nirvanol is not recommended. Table IX summarizes the results in chorea patients whom we have treated. The first five responded favorably to fever therapy. Had complications, such as arthritis, severe carditis, and furuncles not been present in two of the five, the average length of hospitalization from the day of the first treatment to discharge would have been eleven and two-tenths days. This compared favorably with the results obtained with intravenous typhoid-paratyphoid vaccine injections. Patients 6 and 7 were refractory to fever produced both by radiant energy and vaccine. Patient 8, who obtained only moderate improvement, required sedatives on discharge. In patient 5 signs of carditis progressed following fever therapy. Controlled fever, in our opinion, has no advantages over typhoid-paratyphoid vaccine injections in the treatment of chorea; the vaccine is easier to give and the results are as good.

TABLE VIII

ANALYSIS OF CASES OF CONGENITAL SYPHILIS

| CASE NO. RACE, SEX, AGE (YR.) | CONDITION ON ADMISSION TO DUKE HOSPITAL | FEVER TREATMENTS | RESULTS OF THERAPY |
|---|---|---|---|
| (1) 11855 W., ♀, 6 | Wassermann-fast syphilis. No signs of activity of the disease. | Two treatments given at 40.5° C. for 5 and 6 hr. respectively. | Blood serology unchanged one month after last treatment. Treatment was insufficient and period of observation too short. |
| (2) 46332 C., ♀, 3 | Symptomless syphilis. No signs of activity of the disease. Gonorrheal vaginitis and arthritis. | Two 8-hr. treatments at 41.5° C. were followed by alternate courses of bismuth and stovarsol for 2 yr. | Wassermann became negative 1½ yr. after fever therapy. Stovarsol and bismuth given during this period. The gonococcal infection cleared immediately following the fever treatment. |
| (3) 48186 C., ♂, 3 | Untreated syphilis. Wassermann reaction 4 plus. No signs of activity of the disease. | One treatment given at 39.5° C. for 4 hr. Two at 41° C. for 3 to 4 hr., together with 8.9 gm. arsphenamine. | Blood serology unchanged one mo. after last treatment. Treatment insufficient and period of observation too short. |
| (4) 44060 C., ♂, 5 | Paresis. Patient markedly demented. Blood and spinal fluid serology positive; paretic colloidal mastic curve for spinal fluid. | 0.44 gm. (5 doses) arsphenamine followed by fever for 8 hr. at 41.5°, then 0.6 gm. (5 doses) arsphenamine followed by another fever. Five mo. later a similar course of treatment was given. | Spinal fluid findings completely normal 3 days after second treatment. Mental state unimproved. Spinal fluid remained negative. The blood serology was positive. There was considerable improvement in the mental and physical condition after second series of treatments. |
| (5) 51783 C., ♂, 12 | Interstitial keratitis. Failing vision for 2 yr. Opacities of both cornea and exudate in anterior chambers. Slight improvement after 19 gm. of acetarsone (stovarsol). | Fever treatments at 41.5° C. for 8 and 6 hr. respectively. | Definite improvement in vision and decrease of exudate and opacities occurred within period of 12 days. Six mo. later, without further treatment, the patient could barely distinguish large objects. |

TABLE IX

ANALYSIS OF CASES OF CHOREA

| CASE NO. RACE, SEX, AGE (YR.) | CONDITION ON ADMISSION TO DUKE HOSPITAL | RESULT OF FEVER TREATMENTS 40° C. TO 40.5° C. FOR 5 HR. | NO. OF DAYS FROM FIRST TREATMENT TO DISCHARGE |
|---|---|---|---|
| (1) 31744 W., ♀, 12 | Moderately severe chorea of 3 weeks' duration. Apical systolic murmur. | Improvement definite after 2 treatments; almost complete cessation of movements in 9 days. No follow-up. | 9 |
| (2) 35706 W., ♀, 13 | Moderately severe chorea of 2 months' duration, cardiac enlargement, and mitral systolic murmur. Previous attacks of chorea. | Marked improvement immediately following second treatment. Complete recovery in 3 wk. No further cardiac damage noted. No recurrence when seen 4 mo. later. | 9 |
| (3) 60411 W., ♀, 10 | Moderately severe chorea of 2 weeks' duration. | Marked decrease in movements after 2 treatments. Hospitalization continued for 6 days because of furuncles. No follow-up. | 22 |
| (4) 51156 W., ♀, 12 | Severe chorea of 6 weeks' duration. | Almost complete cessation of movements 5 days after second treatment. No recurrence when seen 4 wk. later. | 11 |
| (5) 63299 C., ♀, 4 | Moderately severe chorea of 2 weeks' duration, joint pains, mitral systolic murmur. | One treatment, followed by elevated temperature (rheumatic activity), resulted in clearing of chorea in 11 days. Hospitalization continued 30 days because of arthritis and carditis. No recurrence of chorea when seen 2 mo. later. | 41 |
| (6) 22025 W., ♀, 10 | Moderately severe chorea of 2 weeks' duration. Previous attack refractory to 8 intravenous injections of typhoid-paratyphoid vaccine. | Two treatments caused only slight improvement. No recurrence 6 mo. later. | 15 |
| (7) 47505 W., ♂, 9 | Moderately severe chorea of 10 days' duration. | Two treatments produced slight improvement. Nine intravenous injections of typhoid-paratyphoid vaccine produced no further improvement. No follow-up. | 25 |
| (8) 62464 W., ♂, 6 | Moderately severe chorea of 3 weeks' duration. | Moderate improvement after two treatments. None after the third. Phenobarbital given. No follow-up. | 14 |

MISCELLANEOUS CONDITIONS

*Epilepsy.*—None of 5 children given intravenous typhoid-paratyphoid vaccine had recurrences of seizures after periods of seven to twenty-four months.[43] Sulphur in oil injections caused a reduction in the number of convulsions.[44] The beneficial effects were ascribed to the acidosis, dehydration, and vasodilatation occurring during the fever.

*Intractable Asthma.*—Fifty-one per cent of the thirty-five adults treated at 40° C. (104° F.) for eight hours obtained complete temporary

remissions while 29 per cent had improvement without remissions.[45] Fever therapy is suggested for other allergic conditions.

*Corneal Ulcers.*—Striking improvement was produced by fever therapy in eight cases of corneal ulcer and six of acute iritis.[46]

*Tumors.*—Fever therapy seems to be destructive to the tumor cells and when the type of tumor and the stage of the disease are taken into consideration, most of the patients treated had an increase in the expected length of life.[47]

*Brucellosis.*—Artificial fever apparently was beneficial in 2 of 3 patients.[48]

The effect of artificial fever on many diseases has yet to be determined. It is possible that it may be an aid in treatment of refractory cases of meningococcus meningitis.

Table X is a summary of the miscellaneous conditions we have treated. The decrease in size of the spleen and cervical nodes in the patient with Hodgkin's disease was noted on the morning following treatment. The change was temporary but a similar result was obtained on the second admission. The appearance of jaundice one week after the third treatment suggests that liver disease is a contraindication to fever therapy.

TABLE X

ANALYSIS OF CASES OF MISCELLANEOUS DISEASES

| CASE NO. RACE, SEX, AGE (YR.) | DIAGNOSIS AND CONDITION ON ADMISSION TO DUKE HOSPITAL | FEVER TREATMENTS AND COURSE |
|---|---|---|
| 11747 W., ♂, 8 | Hodgkin's disease of 5 years' duration. Enlarged cervical nodes. Spleen 7.5 cm. below costal margin. Liver enlarged. Anemia and leucopenia contraindicated further x-ray therapy. | Following one 4-hr. treatment at 40.5° C. the cervical nodes were smaller and the spleen only 1 cm. below costal margin. A second treatment 6 days later produced no further change. Three wk. later, patient's condition was as on first admission and treatment resulted in similar changes. Jaundice appeared in 7 days and death occurred 3 mo. later. |
| 59412 C., ♂, 5 | Miliary tuberculosis and tuberculous meningitis. Patient was semistuporous. | Two treatments were given at 41.5° C. for 12 and 9 hr. respectively. Death occurred 16 days after admission. There was no change in spinal fluid or in x-ray appearance of the chest. |
| 61314 W., ♀, 8 | Lymphatic leucemia of 3 months' duration. W.B.C. 738,000 per c.mm. Large doses of Fowler's solution and 6 transfusions given before treatment. | One 12-hr. treatment at 41° C. was given. The W.B.C., dropping rapidly before treatment (738,000 to 5,310), numbered 950 per c.mm. after treatment. |
| 51832 W., ♀, 8 | Acute encephalitis of 12 days' duration. Alternating periods of stupor and hyperactivity. Confused mental state. | Two treatments at 41.1° C. for 8 hr. resulted in immediate definite improvement. Six mo. later patient appeared well but was somewhat backward at school. |
| 24400 W., ♂, 7 | *Brucella suis* infection with remittent fever for two yr.—anemia, leucopenia, and weakness. | Four treatments at 41.5° C. for 5 hr. Two weeks after last treatment death occurred. |

The present early work on fever therapy in tuberculosis seems to indicate that a temperature of 41.5° C. (106.7° F.) for several hours does not kill the tubercle bacillus, although it slows its growth. This form of therapy is not recommended at present in the treatment of tuberculosis. The leucemia patient, already in extremis, died shortly after fever treatment. The child with encephalitis improved soon after treatment; however, the course of the disease is so variable that no conclusions may be drawn from one case. Strains of *Brucella melitensis* vary greatly in their susceptibility to high temperatures[49]; apparently the child that was treated had a highly resistant organism.

## GENERAL CONSIDERATIONS

Severe reactions can be avoided, we believe, by careful observation of the patient before and during treatment. The treatment is a strenuous one under the best of conditions, and should be given only after careful consideration. While we believe the benefits derived from fever therapy outweigh the risks, especially in gonorrheal infections, it should be emphasized that treatment at high temperatures is not devoid of danger. At Duke Hospital approximately four hundred and thirty fever treatments (at temperatures varying from 40 to 41.5° C. [104 to 106.7° F.]) have been given to 280 patients (32 children, 248 adults). Four deaths have occurred (1.4 per cent), all in adults. One of these patients had carcinomatosis with marked involvement of the liver (patient became jaundiced after treatment); the second was debilitated before treatment; the third had a history of heat stroke; and the fourth appeared to be a good risk. If the patient tolerates the first three hours of fever, the remaining two to nine hours of treatment usually will progress smoothly, provided there is an adequate fluid intake, the patient is fairly quiet, and the temperature is not allowed to go above 41.5° C. (106.7° F.).

## SUMMARY

The literature on artificial fever therapy is reviewed and the treatment of 32 children by means of radiant energy is reported. Artificial fever is of value in certain diseases, but it is still in the experimental stage.

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# LISTERELLA MENINGITIS

## A Report of an Additional Case With Necropsy Findings

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A FATAL case of purulent leptomeningitis, due to a new pathogen of the genus Listerella, has been observed in this hospital. Burn[1] in 1933, cultured a hemolytic gram-positive bacillus of the genus Listerella from the blood and lungs of a newborn infant. He subsequently isolated this organism from three other patients and proved them to be identical with two additional strains obtained from other human sources. The case reported here is the seventh in which this bacterium has been isolated. A similar organism associated with suppurative meningitis in cattle has been studied by Jones and Little,[2] and by Seastone.[3]

No definite organisms were seen in direct smears, nor was any growth obtained from cultures of the spinal fluid during life. A subdural abscess was found at necropsy and from this was cultured a gram-positive bacillus which produced beta hemolysis on blood agar. Morphologically and culturally this organism resembled the new species of Listerella described by Burn.[4]

M. B., a three-year-old white male, was admitted to Duke Hospital April 13, 1936, with a history of drowsiness and apathy of four weeks' duration, and of convulsive seizures during the previous two weeks. The family and past histories were noncontributory.

The present illness, initiated by high fever and vomiting, began ten weeks before admission and was thought to be influenza. Two weeks later a diagnosis of pneumonia was made by the family physician. Five weeks after onset the patient was transferred to a neighboring hospital, and the pneumonia cleared rapidly during treatment. While in the hospital otitis media was suspected and a left myringotomy was done but no drainage resulted. Six weeks after onset (four weeks before admission to Duke Hospital) he became lethargic and disinterested in his surroundings and a lumbar puncture was done by his family physician. The cerebrospinal fluid showed 900 cells per cubic millimeter but no organisms were seen. The lethargy increased, and two weeks later the patient began to have muscle twitchings and occasional clonic convulsions characterized by carpopedal spasm and opisthotonos. These convulsions had increased in frequency and had become almost continuous by the time of his admission to Duke Hospital.

*Physical examination* on admission showed an acutely ill, comatose, undernourished, three-year-old white boy, who was markedly spastic and had frequent generalized clonic convulsions. The rectal temperature was 38.9° C. (102.1° F.); pulse rate, 160; and respirations, 60. The skin was hot, dry, and inelastic. The anterior fontanelle was open, measured two by three centimeters, but did not bulge. The suture lines of the skull were slightly separated. Both eyes were deviated to the

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left and there was a ptosis of the left lid. The pupils and fundi appeared to be normal. The left eardrum was dull and injected peripherally. There was slight opisthotonos and moderate stiffness of the neck. The chest was asymmetrical, respirations were rapid, and expansion was poor. The lungs were clear to percussion and auscultation. The abdominal muscles were spastic and the liver edge extended one centimeter below the right costal margin. All extremities, particularly the arms, were spastic. The feet showed marked plantar flexion, and the hands, carpopedal spasm. The bicep and tricep reflexes were not obtained. The knee jerks were present bilaterally, but slightly hyperactive on the right, and there was no ankle clonus. Plantar stimulation produced a suggestive Babinski response bilaterally.

*The accessory clinical findings* were a blood count of 4,960,000 erythrocytes per cubic millimeter, hemoglobin content of 12.4 grams (80 per cent), and 17,000 leucocytes per cubic millimeter, of which 81 per cent were polymorphonuclears (27 per cent nonsegmented), 14 per cent lymphocytes, 4 per cent monocytes, and 1 per cent basophils. The urine was normal. An intradermal tuberculin test (0.1 mg.) was negative. The spinal fluid obtained by lumbar puncture was opalescent, gave a one-plus Pandy reaction, and contained 330 cells per cubic millimeter, of which 63 per cent were polymorphonuclears and 37 per cent lymphocytes. No organisms were seen on direct smear and none could be cultured from the spinal fluid.

Fifteen cubic centimeters of Lederle's polyvalent antimeningococcus serum were given intraspinally. The day after admission his temperature rose to 40.5° C. (105° F.) and pulse, to 200. Seventy cubic centimeters of cerebrospinal fluid were removed by cisternal puncture and 30 c.c. of antimeningococcus serum administered. The cell count on the cisternal fluid was 133 per cubic millimeter.

Several lumbar punctures were done to relieve pressure. In none of these could definite organisms be demonstrated by smear or culture. On one occasion minute gram-negative structures suggesting influenza bacilli were seen on direct smear and 30 c.c. of anti-influenzal serum were given intraspinally. Continuous spinal fluid drainage was instituted on April 16 and meningococcus antitoxin (16,000 units in 140 c.c. of saline buffer solution) was given intravenously on April 17.

A roentgenogram of the chest revealed the lungs to be clear. Chemical analysis of the blood showed: calcium, 10.2 mg. per cent; phosphorus, 3 mg. per cent; carbon dioxide combining power, 45 vol. per cent; and refractive index, 1.3508.

The spinal fluid cell count remained about 150 to 200 until April 16, when yellow-tinged fluid was obtained, which gave a three-plus Pandy reaction and revealed 1,800 cells per cubic millimeter.

The child continued stuporous and his general condition became progressively worse until his death on April 18, five weeks after onset.

### NECROPSY FINDINGS

*Gross.*—On removing the calvarium and opening the dura, a large subdural abscess, measuring 15 by 7 cm., was seen overlying the right cerebral hemisphere causing a marked depression of the frontal and temporoparietal lobes. The abscess cavity was filled with approximately 200 c.c. of yellowish green, moderately thick, purulent exudate. Cultures were made of this material. The abscess was lined by a most unusual, thick, yellow membrane thought to be composed essentially of fibrin, the outer layers of which had undergone organization. Over the left cerebral hemisphere and base of the brain there were numerous collections of purulent material in the subarachnoid space.

On section, the right lateral ventricle was markedly compressed. There was no abscess within the brain tissue itself. One of the larger branches of the middle cerebral artery and the median sagittal sinus were each occluded by a thrombus.

*Microscopic.*—In the subdural space there was an organizing exudate which formed the wall of the abscess. This was continuous with a similar but less extensive process

in the subarachnoid space. Within the organizing tissue there were numerous large, fat-containing, phagocytic, mononuclear cells with small, round, darkly staining nuclei and pale, reticular cytoplasm. There was also a slight diffuse polymorphonuclear neutrophilic infiltration. In the subarachnoid space an occasional area of necrotic cellular débris was present. Bacterial stains showed numerous gram-positive organisms throughout the exudate, which appeared as rounded or bacillary forms in chains. The ventricles and brain tissue itself were not involved in the inflammatory process.

There were several arterial thrombi with an associated slight gliosis throughout the right cerebral hemisphere. The remainder of the necropsy showed nothing of interest.

### BACTERIOLOGIC FINDINGS

Material from the subdural abscess was streaked on a beef infusion blood agar, pH 7.4, plate, and incubated at 37° C. Small colonies, surrounded by a zone of complete hemolysis, were visible within twenty-four hours. The organism was a pleomorphic motile, nonspore-forming gram-positive bacillus, measuring 1 to 4 mu in length and 0.5 mu in breadth. When grown in fluid medium, the bacterium formed short chains.

Dextrose, dextrin, maltose, salicin, galactose, trehalose, and rhamnose were fermented without gas formation after twenty-four hours' incubation; lactose and sorbitol, after seventy-two hours. No change occurred in mannitol, xylose, levulose, inulin, dulcitol, or inositol. Indol was not produced in beef infusion broth and nitrates were not reduced to nitrites.

Serum from rabbits immunized to this new pathogen of the genus Listerella was obtained from Dr. Caspar Burn and agglutinated our strain in a dilution of 1:640.

One-tenth of a cubic centimeter of a 1:10 dilution of an eighteen-hour broth culture injected intravenously into two rabbits caused death within four days. Grossly, no lesions were found, but the organism was recovered from the brain.

### SUMMARY

1. A fatal case of purulent leptomeningitis due to the new pathogen of the genus Listerella is reported.

2. The necropsy and bacteriologic findings are described.

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# STAPHYLOCOCCUS AUREUS MENINGITIS

## Report of a Case With Recovery

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*Staphylococcus aureus* meningitis is so uniformly fatal that each recovery seems worthy of being added to the literature. Schless[1] in 1932 reviewed the literature on *Staphylococcus aureus* meningitis and offered a classification of the clinical types.

The following classification of *Staphylococcus aureus* meningitis is based on that given by Schless.

1. Localized abscess involving the meninges caused by an extension of suppuration from contiguous structures. Numerous recoveries from this type have been reported following surgical intervention.

2. Meningitis accompanied by characteristic evidences of cerebrospinal inflammation, with distinct cerebrospinal changes and with positive cultures of *Staphylococcus aureus*.

   a. Occurring without evidence of staphylococcus septicemia but evidently of hematogenous origin and most frequently secondary to *Staphylococcus aureus* infection in noncontiguous parts of the body.

   b. Occurring with *Staphylococcus aureus* septicemia.

Schless's report deals with a patient who recovered from an infection of the type classified above under 2 a. This recovery followed the introduction of bacteriophage into the spinal canal. Dunlap[2] has since reported a similar case. Stout[3] also reported successfully treating two other cases of *Staphylococcus aureus* meningitis with bacteriophage but sufficient details were not given to allow their classification. Barker[4] reports the only recovery of a patient from the type classified above under 2 b. The following case report also belongs to this type.

W. L. G., a girl, aged two and one-half years, was apparently well until ten days prior to coming under our observation. Irritability and anorexia were the first indications of illness. On the third or fourth day, the child complained of vague abdominal discomfort and the abdomen was found to be slightly distended. By the fifth day the patient became acutely ill. The temperature rose as high as 105° F. orally and a generalized rash developed. The patient was then seen by a physician for the first time. He found, in addition to the above, an injection of the throat. The eruption consisted of fine generalized maculopapular lesions. Scarlet fever was suspected but no confirmatory diagnostic procedures were done and no diagnosis was made. There was no marked change in the child's condition but gradually she became drowsy and slept a great deal. She retained fluids by mouth and obtained some relief of the abdominal distention from frequent small tap water enemas. Stiffness of the neck was first noted the day prior to coming to the hospital at which

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time a lumbar puncture was done. A thick bloody cerebrospinal fluid was obtained and no therapeutic agent was introduced intrathecally.

The patient was admitted to the State University of Iowa Hospitals on July 5, 1935. The history revealed no known exposure to any infectious or contagious disease. Apparently the only possible focus was an infected mosquito bite which was present early during the illness, but this healed without scar before coming under our observation. The family history and past history were irrelevant.

The patient was found to be acutely ill, dehydrated and in marked opisthotonos. She was stuporous except when moved, at which time she became very irritable. The temperature was 105° F. rectally; the pulse, 120; and the respirations, 25. The skin was pale, dry, and inelastic. The lips and mucous membranes also were dry. The tonsils were hypertrophied and slightly injected. The abdomen was moderately distended. Brudzinski and Kernig signs were present. No other abnormal signs were found.

A small amount of thick bloody spinal fluid, requiring withdrawal by syringe, was obtained by lumbar puncture. Smears of this fluid and of that obtained at home revealed gram-positive extracellular cocci, many polymorphonuclear cells and a very few lymphocytic cells. A cisternal puncture was then done and cloudy fluid under increased pressure was obtained. The fluid was withdrawn until it would barely drip and approximately 40 c.c. were obtained. Examination revealed: 1,800 cells per cubic millimeter (96 per cent of which were polymorphonuclear cells); Pandy's test for globulin strongly positive; chemical test for blood, negative; sugar, 60 mg. per 100 c.c.; chlorides, 568 mg. per 100 c.c. Smears of this fluid also revealed gram-positive extracellular cocci. Cultures of all cerebrospinal fluid showed large yellow colonies of *Staphylococcus aureus*. (Cultures were made on ascitic fluid agar, blood agar, chocolate agar, and Sabouraud's agar.) A blood culture was also made and *Staphylococcus aureus* isolated within four days. Blood studies revealed hemoglobin 85 per cent (Sahli); erythrocytes, 4,400,000 per cubic millimeter; leucocytes, 31,800 per c.mm.; 88 per cent neutrophilic cells (42 per cent of which were band forms), 7 per cent lymphocytic cells, 3 per cent endothelial cells and 2 per cent unclassified cells. Fluids were given by mouth, 950 c.c. of fruit juices and water being taken and retained.

Daily progress of the patient was as follows:

July 6, the patient's condition remained essentially unchanged. The temperature ranged between 102.8° and 105.4° F. Since most of the fluids given by mouth were vomited, 500 c.c. of Ringer's solution were given subcutaneously. Cisternal puncture was repeated and 20 c.c. of cloudy fluid were removed. Examination revealed: 5,300 cells per cubic millimeter; globulin test strongly positive; chemical test for blood negative. Cultures of the cerebrospinal fluid were again positive for *Staphylococcus aureus*.

July 7, very little change could be noted in the patient's condition. The temperature ranged between 103° and 104.8° F. Parenteral fluids were administered consisting of 350 c.c. of 10 per cent glucose solution intravenously and 500 c.c. of Ringer's solution subcutaneously.

July 8, the patient became more stuporous but tolerated fluids better by mouth. The skin and mucous membranes no longer showed evidences of dehydration. Four hundred and fifty c.c. (450) of 10 per cent glucose solution were given intravenously. The temperature ranged between 102° and 103.8° F. Roentgenograms of the spine were made but showed no evidence of osteomyelitis.

July 9, the patient became very rigid and more irritable. Temperature ranged between 101.8° and 103.4° F. Gavage of the feedings was started but they were poorly retained. Lumbar puncture was again done and thick bloody spinal fluid was obtained.

July 10, no change could be noted in the patient's condition. The temperature ranged between 101.2° and 104.2° F. Cisternal puncture was repeated and 25 c.c. of cloudy fluid were removed, containing 1,020 cells per cubic millimeter. Cultures were again positive for *Staphylococcus aureus*. A blood culture made at this time showed no growth.

July 11, opisthotonos was more marked but otherwise no change could be noted. The temperature ranged between 101.2° and 103° F. Cisternal puncture was repeated and 38 c.c. of cloudy fluid were removed, containing 1,180 cells per cubic millimeter. Although the patient's condition appeared hopeless, a 250 c.c. blood transfusion was given.

July 12, the patient appeared definitely improved and responded by speaking to her mother for the first time. The temperature ranged between 100.4° and 102.6° F.

July 13, improvement continued and the patient became very irritable. Sedation was started and another 250 c.c. blood transfusion was given. Cisternal puncture was repeated and 40 c.c. of cloudy cerebrospinal fluid were removed, containing 100 cells per cubic millimeter.

Subsequent improvement was gradual but very definite. A cisternal puncture on July 25 revealed a clear fluid and the cell count had decreased to 98 cells per cubic millimeter. Cultures of this fluid were negative. At the time of leaving the hospital (Aug. 8, 1935) there were no abnormal findings except rather marked irritability. An examination on Sept. 23, 1935, revealed a normal child and the home physician reports excellent progress (March 13, 1937).

## SUMMARY

The recovery of a patient from *Staphylococcus aureus* meningitis occurring with *Staphylococcus aureus* septicemia is recorded. The treatment consisted of frequent cisternal drainages to reduce intracranial pressure and general supportive measures, such as parenteral administration of fluids including blood transfusions. This record illustrates that the infection can be self-limited and recovery is possible if life can be maintained through the acute stages of the disease.

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# THE ANTIRACHITIC EFFICIENCY OF IRRADIATED CHOLESTEROL

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THE prolific literature on the different sources of vitamin D is an index of the great interest aroused by this vitamin. Both children and experimental animals can be protected against rickets by direct irradiation, and by ingestion of substances in which the provitamin has been activated by irradiation, or of fish oils naturally endowed with vitamin D. Much recent work has been devoted to comparison of efficiency of these different substances. The most important ones under investigation are irradiated milk, "yeast" milk, fish liver oils, irradiated ergosterol, crystalline vitamin D or calciferol, and irradiated cholesterol. Evidence is accumulating to indicate that irradiated ergosterol is not the active substance or, at least, not the only active form of vitamin D in all of these products.

It seems likely that direct irradiation with ultraviolet rays activates the provitamin of cholesterol in the skin. The provitamin, in turn, is absorbed and protects the individual against rickets. That some substance in the skin is responsible was clearly shown by Hess and Weinstock[1] in the following experiment: "A section of excised human skin was irradiated in the usual manner by means of the mercury vapor lamp and then fed in definite amounts to a series of rats. It was found to confer absolute protection against rickets. On the other hand, similar amounts of skin which had not been irradiated conferred no protection whatsoever. In other words, specific properties had been induced in the skin by means of irradiation, in spite of the fact of its having been deprived entirely of nerve supply and circulation."

It was largely through the investigation of irradiated cholesterol that the early advances in connection with vitamin D were made. Because of the discovery of the high potency of irradiated ergosterol and the great similarity of ergosterol chemically and spectroscopically to the provitamin D of cholesterol, they were generally accepted as being identical. More recent work, however, has shown that many of the previously accepted facts are not wholly true. Bills[2] has recently reviewed the physiology of the sterols and the multiple forms of vitamin D in a

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The assay and preparation of the cholesterol was performed by Dr. J. Waddell. The cholesterol, obtained from the Wilson Laboratories, Chicago, was irradiated and, after irradiation, the activated portion was dissolved in corn oil. Therefore, the preparation was a concentrate of the activated provitamin of cholesterol.

The irradiated cholesterol used in this study was most carefully standardized as to its vitamin D potency. The preparation was assayed by four different laboratories each of which tested it against the U. S. P. reference cod liver oil.

splendid study to which reference may be made. He points out that at present eight different forms of vitamin D have been prepared artificially, and that at least two forms are to be found in the fish oils. The latter forms may or may not be identical with two of the artificially prepared forms.

Waddell[3] in 1934, using the chicken as the experimental animal, found that irradiated cholesterol and cod liver oil were equally effective in preventing rickets, rat unit for rat unit, while irradiated ergosterol had only about one-twenty-fifth the potency on the same basis. This observation has been confirmed by other groups of workers[4] and it is now thought that there are probably three forms of vitamin D obtainable from cholesterol.[5]

Since there is such a pronounced difference in the efficacy of irradiated cholesterol for rats and chickens, it is of interest to consider its effect on infants and this is the object of the present study. In 1927, Hess[6] had already found that rachitic infants could be cured by the addition to the diet of a 3 per cent suspension of irradiated cholesterol in olive oil but of course the unitage was then entirely unknown. He reported, likewise, that 3 teaspoonfuls of a 1.5 per cent solution or 1 gram of irradiated dried brain daily brought about healing. Tisdall, Drake, and Brown[7] reported that in two premature babies 750 I.U. of irradiated cholesterol daily cured acute rickets. Roentgenologically a marked response was demonstrated by the deposition of calcium salts in a period of two weeks. The same investigators[21] in a prophylactic study administered daily 150 I.U. of irradiated cholesterol to a group of seventy-seven white infants. During the course of the winter 8 per cent of these showed signs of extremely slight rickets and 10 per cent showed signs of mild rickets as determined by roentgenologic examinations of the wrists. None developed moderate or marked rickets. These results compared favorably with those obtained in a group of seventy-four white infants who received the same daily dosage of cod liver oil. In a curative study six infants who had moderate rickets were given 750 I.U. daily. Roentgenograms taken two weeks and one month after administration showed signs of marked healing. Three other cases suffering with rickets of the same degree likewise manifested marked healing when given 300 I.U. of irradiated cholesterol daily. Lewis[27] treated three rachitic infants with 435 I.U. of irradiated cholesterol. At the end of four weeks moderate healing had occurred in two infants and marked healing in one infant. The above represents all that is known of the effects of irradiated cholesterol on the rachitic infant.

The present study is divisible into a "preventive" and a "curative" part. The preventive part consists in the report of the attempt to protect a group of babies from rickets by means of the daily administration of irradiated cholesterol. The curative part consists in the report of the attempt, by the same means, to cure slightly developed rickets in

a small group of infants and severe rickets in a still smaller one. The report of the preventive part of the study will be given first.

## THE PREVENTIVE STUDY

*Plan and Conduct.*—The babies included in the preventive study were secured from the dispensary of the Harriet Lane Home of the Johns Hopkins Hospital and from the Welfare Clinics of the city of Baltimore.* In selecting the babies for study the criteria of Eliot and Powers[8] were in general followed, though this was not possible throughout, as that procedure would have reduced the number included considerably. The study was started in October and new babies were accepted until Dec. 6, 1935. Only those were selected who had been born since the previous June 30. They were examined in the clinics once a month for signs of rickets, and measurements of growth were made. The period of observation varied from four to seven months. Feeding instructions were given by the physician in charge of the clinic.

Two full-time social service workers, assisted by two part-time volunteers, visited the homes frequently as well as attended the clinics, so that the infants were seen on the average of every two weeks. Constant vigilance aided greatly in procuring reliable data. During the routine home visits the bottles containing the cholesterol were examined by the workers to see that it was being given regularly. All possible outside sources of vitamin D were checked. About 22 per cent of the infants had received small amounts of antirachitic substances prior to the time of the study. Babies who were bottle fed received fresh pasteurized milk from local dairies. This had not been irradiated. Some babies were breast fed, others bottle fed, and a third group received mixed feedings.

We excluded from the study those cases in which we felt that our information was faulty, cooperation was poor, or other sources of vitamin D, such as cod liver oil, irradiated evaporated milk, or viosterol were given during the period of study.† Some families moved away. Altogether about 27 per cent of the original number were dropped when the final figures were compiled. The number of infants fulfilling requirements were 177. These constituted the material for the preventive study. Almost one-half were colored.

The white and colored infants of the study were distributed as nearly evenly as possible among three groups which were assigned, respectively, dosages of 350, 675, and 950 I.U. of irradiated cholesterol daily. The three different dosages were each supplied in 10 c.c. bottles. The dilutions with corn oil, however, were varied so that the dosage would become uniform and 20 drops in each case contain the desired dose.

*We wish to express our appreciation to Dr. Edwards A. Park for many helpful suggestions and untiring interest, and to the physicians and nurses in these clinics for the help and splendid cooperation extended to us.

†In a study of this nature certain accidental occurrences are bound to arise, principally departures from the prescribed dose of irradiated cholesterol, as administered in the homes.

Glass droppers were furnished with each bottle and were so marked that, when the oil was drawn to the mark, the dropper would deliver 10 drops. Each baby was given 10 drops twice daily. The mothers were instructed to place the tip of the dropper well back on the tongue and expel the contents there. They were shown exactly how to do this by the social worker, who watched the mothers in each home administer the dose on several occasions. By proceeding in this manner we felt that the errors from incorrect dosage were reduced to a minimum.

In spite of these precautions we concluded that the mothers tended to give more than the ordered dosage. By counting the bottles consumed and assuming that the child received all the contents, though we are aware that a small amount was probably lost, it became necessary to regard the three dosage levels as actually advanced somewhat from 350, 675, and 950 I.U. The range of the dose actually administered for each level may be regarded as lying between 350 and 500, 675 and 900, and 950 and 1,200 I.U., respectively.

The diagnosis of rickets, as recorded in this paper, has been made on the roentgenologic basis, as the physical signs in early rickets are often equivocal.[9] All too frequently craniotabes and slight beading, or thickening of the wrists are misjudged or wrongly interpreted and lead to an error in judgment. In the higher dosage groups, x-ray films* of the four extremities including the wrists, elbows, ankles, and knees, were taken at the beginning, middle, and end of the study period; in the lowest dosage group, they were taken at monthly intervals. The final readings of the films were kindly made by Dr. Martha M. Eliot.†

The age and racial distribution of the cases at the start of the study are shown in Table I. Eighty-three per cent of the babies were under

TABLE I

AGE AND RACIAL DISTRIBUTION AT START OF PREVENTIVE STUDY

| | 350 TO 500 UNITS | | 675 TO 900 UNITS | | 950 TO 1,200 UNITS | | TOTAL | |
|---|---|---|---|---|---|---|---|---|
| | WHITE | COLORED | WHITE | COLORED | WHITE | COLORED | WHITE | COLORED |
| Under 6 weeks | 6 | 11 | 7 | 6 | 10 | 6 | 23 | 23 |
| 6 to 10 weeks | 10 | 6 | 14 | 12 | 15 | 9 | 39 | 27 |
| 10 to 14 weeks | 6 | 7 | 13 | 9 | 6 | 4 | 25 | 20 |
| 14 to 18 weeks | 2 | 2 | 2 | 7 | 1 | 3 | 5 | 12 |
| 18 to 22 weeks | | 1 | | | | 2 | | 3 |
| Total | 24 | 27 | 36 | 34 | 32 | 24 | 92 | 85 |

*X-ray technique: General Electric—Snook machine. 2 to 4 cm. of tissue (overlying the bone); 85 K. V. P. (kilovolt peak); 100 M. A. (milliamperes); time 3/20 of a second; distance 36 inches; cardboard holders (nonscreen). The tube used was 3 mm. focus. Broad focus tubes should be avoided.

†The final roentgenographic interpretations were made by Dr. Eliot, according to the following scheme:

A, active progressive rickets without signs of healing.

B, rickets in a state of balance. Evidence of healing, but also continued rachitic activity.

C, healed rickets without evidence of activity.

D, doubtful rickets. Slight departures from the normal which may or may not be early rickets. Still a controversial subject.

E, Normal. No rickets. If rickets has been present the bone has assumed its normal contour.

The degree of rachitic involvement was graded by numbers: 1, slight; 2, moderate; 3, marked; and 4, severe.

TABLE II

DISTRIBUTION OF CASES IN PREVENTIVE STUDY ACCORDING TO DOSAGE, MONTH IN WHICH THERAPY WAS STARTED, AND DURATION OF ADMINISTRATION

| | 350 TO 500 UNITS | | | | | 675 TO 900 UNITS | | | | | 950 TO 1,200 UNITS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TOTAL NUMBER OF PATIENTS | | | | | TOTAL NUMBER OF PATIENTS | | | | | TOTAL NUMBER OF PATIENTS |
| October | | 2 | 20 | 3 | 25 | | 5 | 34 | 7 | 46 | | 4 | 18 | 6 | 28 |
| November | | 17 | 1 | | 18 | 2 | 13 | 7 | | 22 | | 14 | 4 | | 18 |
| December | 2 | 6 | | | 8 | | 2 | | | 2 | 1 | 9 | | | 10 |
| Duration in months | 4 | 5 | 6 | 7 | 51 | 4 | 5 | 6 | 7 | 70 | 4 | 5 | 6 | 7 | 56 |

fourteen weeks of age. Both races were represented, for practical purposes, almost equally, though there were differences in representation at different age levels. The greatest was in the 675 to 900 group at the fourteen to eighteen weeks' level with two white, and seven colored babies listed.

Table II shows the dosage, month in which therapy was started, and the length of time the patient was followed. Since the numbers of colored and white babies in each group were for all practical purposes, equal, they are not tabulated separately. Five were followed for as little as four months and sixteen for as long as seven months; the majority were followed for five or six months.

TABLE III

TYPE OF FEEDING IN PREVENTIVE STUDY

| COLOR AND DOSAGE | PER CENT BREAST FED THROUGHOUT | PER CENT BOTTLE FED THROUGHOUT | PER CENT COMBINATION BREAST AND BOTTLE | TOTAL NUMBER OF CASES |
|---|---|---|---|---|
| 350 to 500 I.U. | | | | |
| White | 29 | 50 | 21 | 24 |
| Colored | 44 | 15 | 41 | 27 |
| 675 to 900 I.U. | | | | |
| White | 22 | 39 | 39 | 36 |
| Colored | 32 | 9 | 59 | 34 |
| 950 to 1,200 I.U. | | | | |
| White | 6 | 78 | 16 | 32 |
| Colored | 37 | 21 | 42 | 24 |

The type of feeding is recorded in Table III, and it is to be noted that breast feeding was considerably more common among the colored than among the white babies. The ratio of colored to white babies was 1 to 3 for bottle feeding and 2 to 1 for breast feeding throughout the period of observation. This is of some interest in view of the distribution of rickets in the two races, as shown in Table V.

TABLE IV

GROWTH AND WEIGHT INCREASE PER MONTH IN PREVENTIVE STUDY

| COLOR AND DOSAGE | AVERAGE WEIGHT GAIN OUNCES | AVERAGE GROWTH INCHES | SMALLEST WEIGHT GAIN OUNCES | LARGEST WEIGHT GAIN OUNCES | SMALLEST GROWTH INCHES | LARGEST GROWTH INCHES |
|---|---|---|---|---|---|---|
| 350 to 500 I.U. | | | | | | |
| White | 21 | 1 | 12 | 27 | 5/8 | 1 3/8 |
| Colored | 19 | 7/8 | 9 | 31 | 5/8 | 1 1/8 |
| 675 to 900 I.U. | | | | | | |
| White | 21 | 7/8 | 14 | 31 | 5/8 | 1 3/8 |
| Colored | 19 | 1 | 11 | 29 | 5/8 | 1 1/8 |
| 950 to 1,200 I.U. | | | | | | |
| White | 21 | 1 | 9 | 32 | 5/8 | 1 3/8 |
| Colored | 18 | 7/8 | 8 | 32 | 5/8 | 1 3/8 |

The growth in length* and the increase in weight, as presented in Table IV, are fairly uniform. The white children averaged 2 to 3 ounces heavier than the colored, but the increases in both growth and weight from month to month in each dosage group are quite comparable.

TABLE V

INCIDENCE OF RICKETS AND DOUBTFUL CHANGES IN X-RAY FILMS IN PREVENTIVE STUDY

| COLOR AND DOSAGE | NUMBER OF INFANTS IN EACH GROUP | PERCENTAGE DISTRIBUTION | | |
|---|---|---|---|---|
| | | SLIGHT RICKETS | DOUBTFUL CHANGES | NORMAL |
| 350 to 500 I.U. White | 24 (9♂ 15♀) | 4 (1 infant, ♀) | 29 (7 infants, 2♂ 5♀) | 67 (16 infants, 7♂ 9♀) |
| Colored | 27 (12♂ 15♀) | 4 (1 infant, ♂) | 15 (4 infants, 3♂ 1♀) | 80 (22 infants, 8♂ 14♀) |
| 675 to 900 I.U. White | 36 (17♂ 19♀) | 0 | 11 (4 infants, 2♂ 2♀) | 89 (32 infants, 15♂ 17♀) |
| Colored | 34 (17♂ 17♀) | 0 | 0 | 100 (34 infants, 17♂ 17♀ |
| 950 to 1,200 I.U. White | 32 (16♂ 16♀) | 0 | 37 (12 infants, 6♂ 6♀) | 63 (20 infants, 10♂ 10♀) |
| Colored | 24 (12♂ 12♀) | 0 | 0 | 100 (24 infants, 12♂ 12♀) |

*Results.*—Table V shows the percentage† distribution of rickets and doubtful changes in the three dosage groups and the distribution in the two races. Looking at the column labelled "slight rickets" it will be seen that only two babies, one colored and one white, developed slight degrees of the disease on the 350 to 500 I.U. dosage, while none on the 675 to 900, and 950 to 1,200 I.U. dosages manifested it.

In the column labelled "doubtful changes" are listed, also, in percentage form, the infants in whose cases the departures from the normal x-ray picture were so slight that one did not feel justified in definitely pronouncing them rachitic. Eliot[10] holds the following opinion concerning them: the evidence points to the fact that the changes described as doubtful are, in reality, the earliest rachitic changes to be seen in the x-ray films. The disappearance of these doubtful changes under continued unaltered treatment indicates that the vitamin D dosage was adequate to repress the disease and to keep it under control. We

*Measurements of length were made with a tape measure from crown to heel, so that they were only approximate.

†Despite the inadvisability of employing percentages when dealing with small numbers it was necessary to use them here because the groups under comparison were uneven in size.

bring up the question of the significance of these doubtful changes again in the discussion, at this point merely stating the facts. Inspection of this doubtful column shows that in the 675 to 900 and 950 to 1,200 I.U. groups none of the colored children showed doubtful rickets, while four, 11 per cent, of the white infants of the 675 to 900 and twelve, 37 per cent, of the white infants in the 950 to 1,200 I.U. group showed them. In the 350 to 500 I.U. group, on the other hand, the colored infants were not exempt from doubtful changes, for four, 15 per cent, showed them. However, in this group, more white infants (seven or 25 per cent) than colored were affected in this way.

At the conclusion of the study the one white baby with active rickets was cured but the one colored baby showing slight rickets had not recovered. Six of the seven white babies in the doubtful class in the 350 to 500 I.U. group had lost their doubtful x-ray signs and two out of the four colored babies had lost them. In the 675 to 900 I.U. group two out of the four, and in the 950 to 1,200 I.U. group eight out of the twelve infants in the "doubtful" groups had recovered.

### THE CURATIVE STUDY

As was to be expected, in the course of selection for the preventive study, infants suffering from slight degrees of rickets and infants showing roentgenologic changes of a doubtful nature were discovered. Their cases are recorded in Table VI and represent infants who were examined roentgenologically coincidentally with those in the preventive study but were at once excluded because of evidence either of rickets, or of possible signs of the disease (doubtful changes). There were al-

TABLE VI

EFFECT OF IRRADIATED CHOLESTEROL IN THE CURE OF RICKETS OF SLIGHT AND MODERATE DEGREE

| DOSAGE AND COLOR | SLIGHT OR MODERATE* ACTIVE RICKETS | DOUBTFUL CHANGES | AVERAGE PERIOD OF TREATMENT MONTHS | PER CENT COMPLETELY HEALED AT COMPLETION OF STUDY |
|---|---|---|---|---|
| 350 to 500 I.U. | | | | |
| White | 3 | 2 | 5 | 100 |
| Colored | 2 | 3 | 5 | 100 |
| 675 to 900 I.U. | | | | |
| White | 2 | 4 | 6 | 66† |
| Colored | 4 | 6 | 5½ | 90‡ |
| 950 to 1,200 I.U. | | | | |
| White | 0 | 3 | 6 | 66§ |
| Colored | 6* | 6 | 6 | 92§ |

*Five of the 6 cases in the 950 to 1,200 I. U. colored group had rickets of moderate degree, rather than slight. They were premature infants and were placed in the high dosage group because we thought that in their own interests they ought to receive liberal amounts of vitamin D.

†In 2 cases doubtful changes persisted at end of study.

‡One case slight rickets, not completely healed, classified as B, at end of study.

§In 1 case doubtful changes persisted at end of study.

together 41 of them; 17 were classified as having "slight active rickets" and 24 as having "doubtful changes." These forty-one infants corresponded in point of age to the infants in the preventive study and were divided into the same three dosage groups and were followed and treated in the same way and roentgenograms taken at the same intervals.

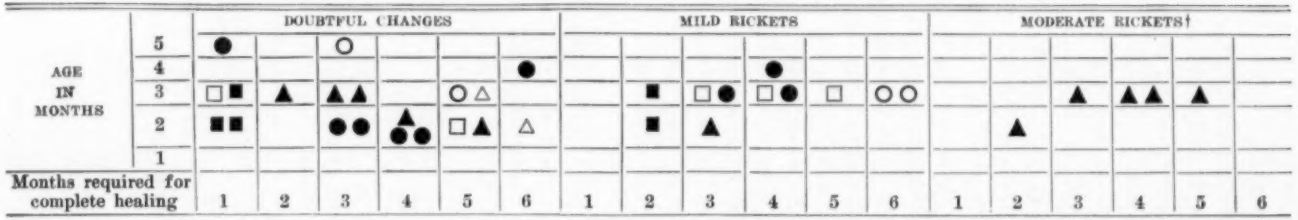
*Results.*—It is of interest to note that of the seventeen infants having rickets all but one were completely cured by the end of the study and of the twenty-four showing doubtful changes all but four had become normal. In the case of the infant continuing to have signs of rickets and in each of the four showing doubtful changes at the end of the study the x-ray films showed definite signs of return toward the normal.

In this small number of curative cases it was not possible to show any correlation between dosage and rate of healing or age of infant. Of the twenty-four babies falling initially in the doubtful group, five showed complete disappearance of the x-ray changes in one month, six more in three months, and nine became normal by the end of the sixth month. In four, doubtful signs were still present at the end of the study. Among the seventeen children showing mild rickets in the initial roentgenograms, again there was no correlation between the three factors. There was, however, slower healing in the higher dosage group. In the 950 to 1,200 I.U. group five out of the six were premature colored infants and all showed moderate degree rather than slight degree rickets. Healing took from two to five months.

In the course of the winter five children suffering with severe rickets came to the Harriet Lane Home and were treated with irradiated cholesterol. Table VII shows the results of the therapy. The histories in regard to previous antirachitic treatment summarized in the table may not be accurate, although the mothers were interrogated on several occasions and each time gave approximately the same story. Healing was spectacular when compared with that ordinarily brought about by two teaspoonfuls of cod liver oil. The results are all the more interesting if credence can be placed on the past histories in three of the cases in which more than the equivalent amount of cod liver oil had been administered for some time. The three infants, E. J., S. J., and V. T. (at the bottom of Table VII), though started on irradiated cholesterol treatment in the middle of March, showed advanced healing before the ultraviolet rays of the sunshine could have been much of a factor.[11] These children were kept indoors most of the time and were advised against any sunbaths during the period of study. In the case of the infant, V. T., the blood serum showed normal calcium and inorganic phosphorus concentrations, in spite of marked clinical and x-ray signs of rickets. It is possible in this case that healing may have started prior to the institution of treatment with irradiated cholesterol.

CHART 1

TIME REQUIRED TO HEAL THE RICKETS COMPLETELY AND TO CAUSE DOUBTFUL CHANGES TO DISAPPEAR*




*In the 350 to 500 I.U. groups, the estimations of the time of complete healing were accurate because of the frequency with which roentgenograms were taken. Since in the case of the two larger dosage groups the x-ray pictures were spaced at longer intervals, the recorded time of healing must have exceeded the actual in a number of instances.

†The five colored premature babies in the 950 to 1,200 I.U. dosage groups had moderate rather than mild rickets.

TABLE VII

CURATIVE EFFECT OF IRRADIATED CHOLESTEROL IN FIVE CASES OF SEVERE RICKETS

| INITIALS AND HISTORY NUMBER | AGE AT BEGINNING OF TREATMENT AND DOSAGE | PREVIOUS ANTIRACHITIC* | EXAMINATION DATES | ROENTGENOLOGIC FINDINGS | BLOOD CA. (12) | BLOOD P. (13) | CA. × P. |
|---|---|---|---|---|---|---|---|
| W. L. C. 96007 | 22 mo. 865 I.U | 4 tsp. C.L.O. from 11/17/35 to 1/21/36. Irradiated milk for 4 mo. prior to start of irradiated cholesterol. Amount not recorded by mother, less than 1 pt. per day. | 1/21/36 | Severe rickets. Questionable healing. | 10.5 | 3.7 | 38.8 |
| | | | 2/11/36 | Marked healing. | 10.0 | 7.0 | 70.0 |
| | | | 3/25/36 | Healing progressively. | 10.6 | 5.3 | 56.1 |
| | | | 4/22/36 | Advanced healing. | 9.5 | 5.6 | 53.2 |
| | | | 5/27/36 | Practically healed. | 10.7 | 6.4 | 68.5 |
| W. G. 95723 | 13 mo. 675 I.U. | C.L.O. ½ tsp. 5/28/34 to 7/28/34. | 12/23/35† | Severe rickets. | | | |
| | | | 1/10/36 | Severe rickets | 9.8 | 3.3 | 32.3 |
| | | C.L.O. 1 tsp. 7/28/34 to 12/23/35. | 2/ 5/36 | Marked healing. | 8.5 | 4.5 | 38.2 |
| | | | 3/10/36 | Healing progressively. | 9.6 | 4.1 | 39.4 |
| | | C.L.O. 2 tsp. 12/23/36 to 1/10/36. | 4/22/36 | Healed completely. | 9.4 | 6.5 | 61.1 |
| | | | 5/28/36 | Healed completely. | 10.6 | 5.5 | 58.3 |
| E. J. 96628 | 14 mo. 675 I.U. | 3 tsp. C.L.O. daily for 7 days, started 3/4/36. Condensed milk formed major part of diet before treatment was begun. | 3/11/36 | Severe rickets. | 8.8 | 3.8 | 33.4 |
| | | | 3/25/36 | Slight healing. | 10.4 | 3.8 | 39.5 |
| | | | 4/22/36 | Marked healing. | 9.0 | 5.4 | 48.6 |
| | | | 5/27/36 | Healing progressively. | 9.9 | 5.0 | 49.5 |
| | | | 6/30/36 | Definitely improved, not quite healed. | 9.4 | 4.5 | 42.3 |
| S. J. 90642 | 16 mo. 675 I.U. | 2 tsp. C.L.O. daily for the past year. | 3/17/36 | Severe rickets. | 9.9 | 4.1 | 40.6 |
| | | | 4/22/36 | Marked healing. | 8.9 | 6.1 | 50.1 |
| | | | 5/28/36 | Healing progressively. | 10.0 | 6.4 | 64.0 |
| | | | 6/25/36† | Definitely improved, not quite healed. | | | |
| V. T. 90119 Colored | 17 mo. 675 I.U. | No antirachitic, other than small amounts of irradiated evaporated milk given irregularly. | 3/ 2/36 | Severe rickets, with slight healing. | 10.0 | 5.8 | 58.0 |
| | | | 3/25/36 | Marked healing. | 10.5 | 5.6 | 58.8 |
| | | | 4/22/36 | Healing progressively. | 9.4 | 5.5 | 51.7 |
| | | | 5/28/36 | Practically healed. | 10.9 | 6.2 | 67.6 |
| | | | 6/24/36 | Completely healed. | 10.0 | 5.7 | 57.0 |

*Histories, in all probability, not very reliable.
†No calcium and phosphorus determinations made.

## DISCUSSION

The conditions of the study have all been given and hence will not be repeated here.

The essential result in the preventive study was that only two infants among the 177 treated with irradiated cholesterol developed rickets while under treatment and this in a very slight degree. Both were in the low dosage (350 to 500 I.U.) group. By the end of the study all signs of the disease shown in the early x-ray films had disappeared in the case of one, the white baby, but not in the case of the other, the colored baby. This result we consider quite remarkable in view of the small dosage of irradiated cholesterol used.

As already stated, the opinion of Dr. Martha M. Eliot is that the infants whose films were classified as doubtful, in the great majority of instances, at least had incipient rickets and for practical purposes ought to be so regarded. However, if such is the case, there are curious discrepancies. First, no colored infants in the 950 to 1,200 I.U. and the 675 to 900 I.U. dosage groups showed these changes, whereas twelve white infants in the 950 to 1,200 I.U. and eleven infants in the 675 to 900 I.U. dosage groups showed them. Moreover, though in the 350 to 500 I.U. dosage group four colored infants presented these doubtful changes, seven white infants showed them. One might have expected that if these doubtful changes were really rachitic in nature, the colored infants would have been more affected than the white infants. That the natural incidence of rickets among our babies was greater among the colored than the white is indicated in the curative study, for in it the colored infants predominated over the white ones 12 to 5. This predominance of the colored occurred even though breast feeding was more common among the colored infants, as already brought out. In the second place the protection from these doubtful changes did not increase proportionately with the dosage of the irradiated cholesterol, as one might have expected, if the changes had been rachitic. For example, in the 950 to 1,200 I.U. dosage group one might have expected that the protection from rickets would have been complete. But actually 37 per cent of the white babies showed these doubtful changes. If the doubtful changes were rachitic in nature, the natural induction to be drawn from our data would be that the disease in the colored infant is more readily blocked and prevented by the oral administration of vitamin D than is the disease in the white infant, and such actually may be the case though the idea is the opposite of the conception generally held. In view of the facts given we have decided that it is best merely to state the occurrence of the doubtful changes and not to draw any conclusions concerning them.

The outcome in the curative study of seventeen infants showing very slight degrees of rickets was as striking as in the preventive study. Of

the seventeen infants showing slight evidences of the disease in the x-ray films when treatment with irradiated cholesterol was begun all but one were completely cured by the end of the study and in the case of the one refractory baby signs that the disease was in process of regression could be seen in the last x-ray films taken. In this curative study twenty-four infants showed the doubtful changes. At the end of the study the changes had disappeared in all but four and in those four the x-ray films showed that regression toward the normal was in progress.

The results in the case of the five children suffering from severe rickets furnished practical evidence that the irradiated cholesterol possessed excellent potency, for in all five cases the cure of the disease rapidly followed the administration of the drug.

A comparison of the results of this study and of other preventive studies with each other would be of the greatest possible interest, but is fraught with difficulties, since in each of the studies a special set of conditions existed which did not hold in the other studies and made comparison impossible or difficult. Differences in sex, age, and race, the dosage of antirachitic substance employed, the medium in which it was carried, the length of the period of observation, the frequency with which x-ray films were taken, the standards of interpretation of the pictures, and, finally, in the closeness with which the infants were supervised introduce great confusion, when the attempt is made to bring the results into comparison. Nevertheless we have listed the results in several of the most significant studies in Table VIII and we make the following general statements based upon them.

Beginning with our own preventive study only two infants out of 177 developed rickets and both were in the lowest dosage group of 350 to 500 I.U. In the studies conducted by Eliot and her coworkers[10] and in those of Drake, Tisdall, and Brown[24] a higher incidence of rickets occurred in the groups of infants given cod liver oil, viosterol in milk, and viosterol in oil in dosages averaging between 350 and 540 I.U. than developed in our series.

In the experiments of Eliot and coworkers, and Tisdall, Drake, and Brown, cod liver oil and viosterol in dosage levels ranging from 675 to 825 I.U. appeared inferior to irradiated cholesterol in dosages ranging between 675 and 900 I.U. for the prevention of rickets.

In the studies listed the various antirachitic substances employed, when administered in dosages from 1,050 to 1,450 I.U. daily, show a greater degree of protection than when given in lower dosage levels. Irradiated cholesterol in oil in our experiment completely prevented rickets in the 950 to 1,200 I.U. dosage. Shelling and Hopper[20] and Lewis[15] reported practically complete absence of rickets in their groups of infants treated with viosterol and with crystalline vitamin D in oil. Cod liver oil and viosterol gave about 80 per cent protection in dosages

TABLE VIII

COMPARISON OF THE EFFICIENCY OF VARIOUS ANTIRACHITIC SUBSTANCES AT LOW, INTERMEDIATE, AND MODERATE DOSAGE LEVELS

| TYPE OF ANTIRACHITIC AND MENSTRUUM | COLOR AND DOSAGE | PERCENTAGE DISTRIBUTION | | | NUMBER OF INFANTS | AGE AT BEGINNING OF STUDY | INVESTIGATORS |
|---|---|---|---|---|---|---|---|
| | | RICKETS | DOUBTFUL | NORMAL | | | |
| C.L.O. | White 460 I.U. | 37 | 47 | 16 (63) | 19 | Under 69 days | Eliot et al. |
| C.L.O. | White 350 I.U. | 29 | Not recorded | 71 (71) | 14 | Under 4 mo. | Drake, Tisdall, and Brown |
| C.L.O. | Colored 470 I.U. | 27 | 27 | 46 (73) | 15 | Under 69 days | Eliot et al. |
| C.L.O. conc. in milk | White 400 I.U. | 17 | 23 | 60 (83) | 30 | Under 69 days | Eliot et al. |
| C.L.O. conc. in milk | 3 colored, 25 white Av. 243-367 | 10 | 87 | 3 (90) | 28 | Under 13 wk. | Wilson.[17] Study includes 2 sets of twins and 1 premature. |
| C.L.O. conc. in milk | Colored 400 I.U. | 30 | 10 | 60 (70) | 10 | Under 69 days | Eliot et al. |
| Crystalline vit. D in milk | 53% colored 290 I.U. | 1.9 No severe | Not recorded | 98.1 | 51 | 2 wk. to 5 mo., Av. 3.2 | Lewis |
| Crystalline vit. D in oil | 58% colored 290 I.U. | 9.6 One severe | Not recorded | 90.4 | 52 | 2 wk. to 5 mo. Av. 3.0 | Lewis |
| Crystalline vit. D in propylene glycol | 58% colored 290 I.U. | 11.1 No severe | Not recorded | 88.9 | 45 | 2 wk. to 5 mo. Av. 3.0 | Lewis |
| Viosterol in milk | White 400 I.U. | 21 | 21 | 58 (79) | 29 | Under 69 days | Eliot et al. |
| Viosterol in milk | Colored 400 I.U. | 14 | 5 | 81 (86) | 21 | Under 69 days | Eliot et al. |
| Viosterol in oil | White 540 I.U. | 31 No severe | Not recorded | 69 | 29 | Under 4 mo. | Drake, Tisdall, and Brown |
| Yeast milk | White 400 I.U. | 30 | 10 | 60 (70) | 30 | Under 69 days | Eliot et al. |

TABLE VIII—CONT'D

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Yeast milk | Colored | 400 I.U. | 27 | 27 | 46 (73) | 11 | Under 69 days | Eliot et al. |
| Irr. cholesterol in oil | White | 350 I.U. | 4 | 29 | 67 (96) | 24 | Under 18 wk. | Present study |
| Irr. cholesterol in oil | Colored | 350 I.U. | 4 | 15 | 81 (96) | 27 | Under 22 wk. | Present study |
| C.L.O. | White | 659 I.U. | 45 | 20 | 35 (55) | 40 | Under 69 days | Eliot et al. |
| C.L.O. | White | 821 I.U. | 65 | 12 | 23 (35) | 17 | Under 69 days | Eliot et al. |
| C.L.O. | Colored | 652 I.U. | 41 | 15 | 44 (59) | 34 | Under 69 days | Eliot et al. |
| C.L.O. | Colored | 789 I.U. | 30 | 10 | 60 (70) | 10 | Under 69 days | Eliot et al. |
| C.L.O. | White | 700 I.U. | 40 | Not recorded | 60 | 15 | Under 4 mo. | Tisdall, Drake, and Brown |
| Viosterol in oil | White | 689 I.U. | 46 | 4 | 50 (54) | 22 | Under 69 days | Eliot et al. |
| Viosterol in oil | Colored | 678 I.U. | 24 | 16 | 60 (76) | 25 | Under 69 days | Eliot et al. |
| Irr. cholesterol in oil | White | 675 I.U. | 0 | 11 | 89 (100) | 36 | Under 18 wk. | Present study |
| Irr. cholesterol in oil | Colored | 675 I.U. | 0 | 0 | 100 | 34 | Under 18 wk. | Present study |
| Viosterol in oil | White | 1,392 I.U. | 33 | 33 | 33 (66) | 24 | Under 69 days | Eliot et al. |
| Viosterol in oil | Colored | 1,361 I.U. | 4 | 23 | 73 (96) | 26 | Under 69 days | Eliot et al. |
| Viosterol in oil | White | 1,080 I.U. | 22 | Not recorded | 78 | 27 | Under 4 mo. | Drake, Tisdall, and Brown |
| Viosterol in oil | White | 1,125 I.U. | 0 | Not recorded | 100 | 42 | Under 5 mo.* | Shelling and Hopper |
| Viosterol in oil | Colored | 1,125 I.U. | 2 | Not recorded | 98 | 133 | Under 5 mo.* | Shelling and Hopper |
| Crystalline vit. D in oil | 21% colored | 1,450 I.U. | 2.1 | Not recorded | 97.9 | 42 | 2 wk. to 5 mo. Av. 3.1 | Lewis |
| C.L.O. | White | 1,050 I.U. | 23.4 (1 severe) | Not recorded | 76.6 | 17 | Under 4 mo. | Drake, Tisdall, and Brown |
| Irr. cholesterol in oil | White | 950 I.U. | 0 | 37 | 63 (100) | 32 | Under 18 wk. | Present study |
| Irr. cholesterol in oil | Colored | 950 I.U. | 0 | 0 | 100 | 24 | Under 22 wk. | Present study |

*The majority under 5 months.

of 700 and 1,080 I.U. respectively in a study by Drake, Tisdall, and Brown.[16] The white and colored groups differed widely in their susceptibility to rickets and in their resistance to antirachitic therapy. In the investigation of Eliot and her coworkers[10] 33 per cent of the white children and 4 per cent of the colored developed evidence of the disease when receiving daily dosages of 1,361 to 1,392 I.U. of viosterol daily.

Now turning to work not recorded in Table VIII, Barnes[18] reported complete protection in a series of infants given only 125 I.U. of cod liver oil concentrate in milk. Drake, Tisdall, and Brown[21] have reported that of seventy-seven white babies varying in age from one to six months at the beginning of treatment with 150 I.U. of irradiated cholesterol, 10 per cent developed mild rickets. Similar groups given plain cod liver oil or percomorph oil in the same dosage developed approximately the same incidence of mild rickets. Lewis[14, 15] has recently emphasized both by curative and preventive study the importance of the menstruum in which the antirachitic substance is provided. In a preventive study, when crystalline vitamin D was administered at a 290 I.U. level in milk, in corn oil, and in propylene glycol, 1.9 per cent, 9.6 per cent, and 11.1 per cent of the infants developed rickets. One severe case developed when the oil menstruum was used.

Soer,[19] conducting a study in Holland treated five hundred and forty-four children prophylactically in the course of three winters with "substance L" amounting to 800 I.U. daily mixed with cocoa butter. Only four of this entire group who were treated regularly developed rickets. The diagnosis was based on monthly physical examinations and roentgenograms. The age incidence is not mentioned.

Irradiated milk when given in quantity which supplies daily doses of from 100 to 200 I.U. of vitamin D affords good, though not complete protection, for colored and white infants. This has been shown by the work of Hess and Lewis,[22] Mitchell, Eiman, Stokes, and Whipple,[23] Drake, Tisdall, and Brown,[24] Rapoport, Stokes, and Whipple,[25] and Eliot and coworkers.[10] Whether the potency of irradiated milk is due solely to the effectiveness of the contained irradiated cholesterol, or whether the menstruum furnished by the milk is particularly favorable and hence is a factor, is a matter of great interest which should be investigated further.

## SUMMARY

An outpatient preventive study to test the efficiency of irradiated cholesterol dissolved in corn oil was conducted upon one hundred and seventy-seven nonrachitic infants varying in age at the beginning of observation from one to five months with the majority under three and one-half months. This study covered in each instance from five to seven months. Ninety-two of the infants were white, eighty-five colored. The infants were divided into three groups. The racial distribution in them

was made as nearly equal as possible. The dosages assigned for the three groups were 350, 675, and 950 I.U., respectively, but since in many instances more of the mixture of irradiated cholesterol in corn oil was given than prescribed, the three dosages actually given may be regarded, in the lowest group, as lying between 350 to 500 I. U., in the intermediate group, between 675 to 900 I.U., and in the highest group, between 950 to 1,200 I.U. The striking results in this preventive study were that only two infants, one white and one colored, developed rickets which was in both instances of an extremely slight degree. Both infants were in the lowest dosage group.

In the case of twenty-seven infants in this preventive study there were observed in the x-ray films at the lower ends of the radius and ulna slight deviations from the usual. We could not be certain that the deviations denoted incipient rickets, on the one hand, or that they were not within the range of normal variation, on the other. We termed them doubtful changes. If they were rachitic they must have represented degrees of the disease so slight as to be, practically speaking, meaningless. In nineteen instances these doubtful changes disappeared under treatment and in eight instances they were still present at the end of the study. It is interesting that they occurred chiefly in the white babies; in the two higher dosage groups they were exclusively in the white babies, and in the lower dosage group were more numerous in the white (7 to 4) than in the colored babies. Since we do not know the nature of these doubtful changes we state the facts concerning them without attempting to draw any conclusions.

Two curative studies to test the effectiveness of the irradiated cholesterol were conducted in addition to the preventive test. When babies for the preventive study were being examined, in order to make certain that rickets was not present, forty-one were found who showed either incipient rickets or else deviations from the classical normal at the lower ends of the radius and ulna which we were unable to interpret and hence called doubtful. These forty-one infants obviously could not be placed in the preventive study and were used for the curative test. They were of the same age as the infants in the preventive study and were divided into three groups and given irradiated cholesterol in the same dosages as those used in the preventive study. The period of treatment and observation was also the same as in the preventive study, namely, five to six months. Seventeen of the forty-one infants exhibited slight or moderate degrees of rickets when the treatment with irradiated cholesterol in corn oil was begun. In all seventeen instances except one a cure was effected by the time the study was complete and in that one exception signs of regression of the disease were in evidence in the x-ray films taken as the study drew to a close. Twenty-four of the forty-one infants showed doubtful changes in the x-ray films. In all but four in-

stances the doubtful changes entirely disappeared in the course of the study and in two of the four, signs of regression of the signs could be seen in the last x-ray films. Again we give the facts but draw no inferences from this doubtful group.

In the second curative test the group of rachitic subjects was exceedingly small, consisting of five infants, but the rickets was severe. Well-marked healing showed itself in the x-ray films within a month following the administration of either 675 or 865 units of irradiated cholesterol daily.

The results of some of the other studies recorded in the literature which were similar to our studies are presented together with ours in chart form. Comparison of the results obtained suggests that the efficiency of irradiated cholesterol in oil in protection from rickets is excellent. The results seem equal or possibly superior to those obtained with other antirachitic substances in oil when administered at a dosage level of approximately 400 or 775 I.U. Our cases in the curative tests were too limited in number to permit conclusions of a comparative nature based on past experience with cod liver oil or viosterol. But we gained the impression that irradiated cholesterol was a powerful antirachitic substance, fully the equal of viosterol or cod liver oil, unit for unit, and perhaps superior.

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# SUDDEN DEATH DUE TO MERCURIAL DIURETICS

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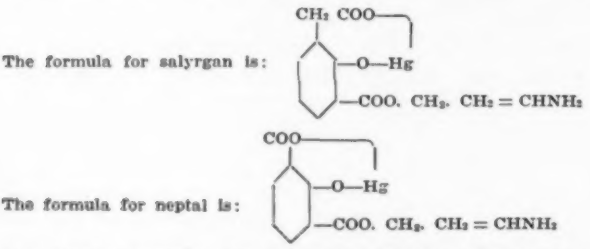
THE first of the mercurial diuretics to attain common use because of its excellent diuretic effect was novasurol. In 1925 novasurol was displaced by salyrgan and later by neptal which were found to be much less toxic and to have a better diuretic effect.* Since then many reports[1]




It is obvious, however, that the active radicals in both drugs are identical. In salyrgan the acetate radical is introduced to increase the solubility of the compound in water; in neptal the carboxylic acid radical renders the compound equally soluble and is used instead of the acetate merely for trade purposes. Neither radical has any pharmacologic action. Pharmacologically there is no difference in the two drugs.

have appeared of patients to whom salyrgan was given over a period of years without toxic manifestations or without diminution of its effectiveness. It has also been pointed out that the only disadvantages of neptal or salyrgan are first, that it is valueless when given per os, second, that it has a tendency to produce venous thrombosis at the site of injection when administered intravenously, and third, that it causes pain when administered intramuscularly. Consequently, because of its excellent diuretic effect and because of the general belief that significant toxic sequelae following its repeated administrations do not occur, salyrgan has become a widely used diuretic drug. The purpose of this paper is to show that this belief is erroneous and that, at certain times and under certain conditions, sudden death may follow the intravenous injection of the drug.

That death following the intravenous use of neptal is not extraordinarily infrequent may be seen from the fact that the death of the two patients whose cases are reported here occurred during the same year.

CASE 1.—A white, male, two-year-old child was admitted to the pediatric service of the Israel Zion Hospital on Aug. 11, 1936, with the chief complaint of generalized edema of five months' duration. The mother stated that the edema was preceded by a "cold" and an elevation of temperature for one day. Physical examination

From the Pediatric Service of the Israel Zion Hospital.

*The terms of neptal and salyrgan are used synonymously throughout this communication although the two preparations are not identical.

showed a pale child with marked pitting edema of the face, abdomen, scrotum, and lower extremities. Evidence of fluid in the right pleural cavity was present. The temperature was 98.6° F. The blood pressure was 102 systolic and 74 diastolic. The abdomen was markedly distended and the superficial veins were prominent, and marked ascites was present. Fundi examinations on several occasions were negative.

*Laboratory Findings.*—The urine showed the presence of a large amount of albumin, a moderate number of red and white blood cells, and a few granular casts. Examination of the blood showed 3,400,000 red blood cells, a hemoglobin content of 65 per cent (Sahli), a white blood count of 10,600, with an approximately equal distribution of polymorphonuclear leucocytes and lymphocytes; the total nonprotein nitrogen was 51.6, the urea nitrogen 38.8, the creatinine 2.42, uric acid 4.82, and cholesterol 218 mg. per cent. The total proteins of the serum were 6.31 gm. per cent; the serum albumin was 3.66, and the serum globulin 2.64 gm. per cent; the albumin-globulin ratio was 1.38:1. Throughout the child's stay in the hospital his blood pressure averaged 90 systolic and 60 diastolic. The Wassermann reaction was negative. One month after admission to the hospital examination of edema fluid withdrawn from the dorsum of the foot revealed an albumin content of 1.124, a globulin content of 0.106 gm. per cent, and an albumin-globulin ratio of 10.6:1. The chloride content of the edema fluid was 406.4 mg. per cent. Several determinations of the serum protein content of the blood were made during the child's stay in the hospital and at no time was the total serum protein at or below the critical level at which edema develops (5.25). Similarly, at no time did the serum-globulin fraction exceed the albumin in amount, nor was there any close relationship between the serum proteins and the degree of edema.

A diagnosis of nephritis with a nephrotic component was made.

*Course.*—The edema increased in spite of treatment with diuretin, aminophyllin, desiccated thyroid, calcium gluconate, and a mixture of citrates. Two transfusions of 100 c.c. each of whole blood were given without benefit. On October 1, 0.5 c.c. of neptal was given intramuscularly. Twenty-four hours later diuresis set in and there was a loss of four pounds in weight, with a decided improvement in the child's general condition. On October 5, 1 c.c. of neptal was again given intramuscularly but without the beneficial effects observed after the first administration of the drug. On October 12 it was decided therefore to inject neptal intravenously. One c.c. was injected intravenously and one minute later the child became dyspneic and cyanotic, the pupils became widely dilated, the pulse imperceptible, and the child died.

*Necropsy Findings.*—(Dr. J. M. Ravid.) Pathologic-anatomic diagnosis: nephrosis with generalized anasarca, ascites, hydrothorax, and hydropericardium; calcium deposits in the kidney tubules; hepatomegaly, with absence of glycogen; cerebral congestion and edema; lymphoid hyperplasia of the mesenteric glands and Peyer's patches; enlarged spleen. (Only the organs showing definite changes will be described in detail.)

The body was that of a well-developed, waterlogged, white, male child about two years old; the weight was 20 kg. and the length 81 cm. On incising the abdomen, it was noticed that the subcutaneous structures were moist and on opening the peritoneal cavity a large amount of clear, serous fluid gushed out, under pressure. The amount was estimated to be three liters. Several hundred c.c. of clear serous fluid were found in both pleural cavities and about 100 c.c. in the pericardial cavity. The heart occupied the usual position, was normal in size, weighed 58 gm., and measured 7 by 5 by 3 cm. The left side of the heart was contracted in systole, the right side was flabby and dilated. On section, the myocardium was pale pink in color and soft in consistency. The left ventricle measured 13 mm., and the

right, 5 mm. in thickness. The lungs were normal in size, were crepitant throughout, and no areas of gross consolidation could be felt. On section, the cut surface was pink, smooth, and homogeneous in appearance. On pressure, a quantity of thin, frothy, slightly sanguineous fluid could be expressed. The spleen was enlarged, weighed 98 gm. and measured 10 by 7 by 4 cm. On section, the parenchyma was firm, the pulp scraped off with ease, and the malpighian corpuscles were prominent.

The liver was enlarged, weighed 834 gm., and measured 19 by 17 by 8 cm. The capsule was smooth, glistening, and pinkish red in color. On section, the parenchyma was firm, the lobules could be made out with ease, and irregular, scattered, yellowish areas could be detected here and there. In the lower half of the small intestines, i.e., in the ileum, the solitary lymph follicles were prominent. The mesentery presented a large number of pinkish red lymph glands, varying in size from that of a pea to that of an almond. These glands were firm and, on section, presented a smooth, pink, homogeneous surface on which a paler cortical layer was evident.

The kidneys presented a remarkable appearance. The left kidney was enlarged, weighed 110 gm., and measured 85 by 50 by 45 mm. The capsule stripped with ease, exposing a marked fetal, lobulated surface which was smooth and glistening. The entire surface was studded with pinhead-sized petechial specks alternating with pea-sized grayish pink areas, giving the impression of a surface sprinkled with red pepper. On section, the same petechial mottling was observed throughout. The parenchyma was smooth and glistening and the renal markings were well defined. The cortex did not appear narrowed and the normal ratio of cortex to the medulla was present. Cortical markings were well defined and continued down between the pyramids. A similar petechial appearance was noticed in the lining of the pelvis. The right kidney weighed 103 gm. and was similar in every respect to the left one; it measured 82 by 47 by 77 mm.

The brain was very edematous; the sulci were flattened and the gyri narrowed and shallow.

*Microscopic Findings.—Lungs:* Alveolar spaces were widened in most places, the septal walls thin, except in a few areas where some collapse and partial aeration were present.

*Liver:* The lobulations were poorly outlined, the cells were swollen and showed everywhere a complete absence of glycogen, as evidenced by the vacuolated appearance of the cells. A number of periportal spaces showed a small collection of round cells.

*Kidneys:* Examination of the glomeruli showed endothelial swelling with a slight increase in the number of endothelial nuclei and fusion of many of the capillary loops. The intervening capillary loops showed a marked congestion and an enormous distention of the capillaries. The glomerular segments were widened; no polymorphonuclear leucocytes, round cells, or other types of cells were seen. There were no proliferative changes whatever either within the loops or in the Bowman capsular lining. Only a few Bowman's capsules showed slight thickening. The glomerular spaces throughout showed a moderate amount of albuminous débris, some in the form of hyalin droplets. The proximal tubules showed various transitions from complete degenerative changes to practically normal cell outlines. In places the tubules showed beginning atrophy with a consequent widening of the interstitium. In other places early hyperplasia with well-preserved, tall, columnar, active epithelium could be seen. Many of the partly degenerated proximal tubules contained hyalin casts and had low cuboidal and flattened epithelium. Some of these were cystically degenerated and contained large amounts of albuminous material, usually in the form of a cast, within their lumens. The interstitium, in the region of the proximal tubules, was irregular and in places considerably broadened with a peculiar

myxomatous connective tissue, and contained, in addition to a few fibroblasts, numerous round cells, some macrophages, and occasional polymorphonuclear leucocytes. The interstitium was also broadened within the medulla. Near the cortex and particularly at the surface, a number of focal, dense, round cell infiltrations could be seen. Scattered throughout the cortex and medulla were a number of tubules which showed calcium deposits, some calcification, and a complete loss of outline. Thus it may be seen that the changes were predominantly tubular with subsequent calcification as a result of previous necrosis and degeneration. The capillaries, both in the cortex and in the medulla, were clustered into groups and showed marked congestion. Grossly, these appeared as minute hemorrhages but no hemorrhage throughout the cortex and medulla could be noticed.

CASE 2.—(This case is reported through the courtesy of Dr. Harold Hermann.) A white, male child, three years old, was admitted to the hospital on Aug. 10, 1935, with a diagnosis of nephrosis. During all of August and half of September he was treated with a high protein diet and the internal administration of 8 gr. of desiccated thyroid a day. On September 14 he was discharged improved but was readmitted on Oct. 1, 1935, because of extensive edema of the eyelids, ankles, and abdomen. The mother stated that his condition had been good for three days after he left the hospital but that from that time until his readmission the edema had progressively increased. She also said that until three days prior to his second admission he had urinated frequently and in fairly large amounts but that for three days before admission there was a marked diminution in the output of urine.

Physical examination revealed pallor, generalized anasarca, and ascites. Otherwise the examination was negative. The blood pressure was 120 systolic and 60 diastolic. Urine examination showed a large amount of albumin and the absence of red blood cells. The white blood count was 10,000 with 68 per cent polymorphonuclear leucocytes. Blood examination showed cholesterol 186, urea nitrogen 18.6, uric acid 3.84, creatinine 1.62 mg. per cent. Subsequent examinations of the blood revealed essentially the same findings. On Aug. 28, 1935, the total serum protein was 5.812 gm. per cent; the albumin content 3.224 gm. per cent, and the globulin 2.588 gm. per cent. On Oct. 21, 1935, the serum protein was 5.884 gm. per cent, the albumin content 3.880 gm. per cent, and the globulin 2.004 gm. per cent. The albumin-globulin ratio was 1.936:1.

On October 10 the child was given 0.5 c.c. of neptal intravenously; following this, the urinary output increased, with a disappearance of some of the edema. On October 15, 4 gr. of desiccated thyroid and 5 gr. of ammonium chloride were given three times a day. On October 16, 0.5 c.c. of neptal was given intravenously with no ill effects. On October 19, 0.5 c.c. was again given intravenously. This injection was followed in two minutes by a convulsion, coma, cyanosis, and stertorous breathing. Oxygen inhalations were given, adrenalin was injected intracardially, and artificial respiration was employed, all with no benefit. The patient died within five minutes after the injection. Autopsy was not done.

## COMMENT

Careful search of the literature reveals two other reports of death following the injection of mercurial diuretics. One was the report by Wolf[2] of a boy four years old who suffered from nephrosis. Previous to the fatal dose, he had received five injections of salyrgan intravenously. Each injection was followed by an augmented rise in the afternoon temperature. The resulting urinary output was poor; the injection preceding the fatal administration caused chills, fever, a morbilli-

form rash, anorexia, and malaise. The sixth injection caused sudden death. Wolf believed that the death was an anaphylactoid one. Unfortunately, no postmortem examination was done.

The second report was by Molnar.[3] His patient was thirty-nine years old and suffered from ascites, syphilitic aortitis, and aortic insufficiency. The patient was given 2 c.c. of novurit intraperitoneally and complained of intense abdominal pain immediately after the injection. Twenty to twenty-five minutes after the injection he became dyspneic and cyanotic, and died. Autopsy showed the presence of luetic aortitis but failed to explain the sudden death. Molnar believed, however, that his patient died because of hypersensitiveness to the drug.

In spite of the small number of reports, we feel that sudden death occurs more often following the intravenous injection of neptal or salyrgan than one has been led to believe. It is quite understandable that we are more prone to publish reports of good results with some new form of therapy and are reluctant to report the bad results, particularly if death occurs. It is interesting to note that death occurred in all cases in about the same manner and that all four patients showed marked dyspnea and cyanosis. In addition, one patient had convulsive seizures.

The autopsy findings in our first case point to the fact that the death was probably an anaphylactoid one. Waldbott[4] stated that, when an antigen is introduced into the venous system, the capillary circulation of the lungs, which is the first to be reached by the antigen, becomes principally involved and shows the changes which he described as occurring in anaphylactoid death, namely—capillary congestion and edema with subsequent cellular infiltration. He states further that, in careful examination of patients who probably died of anaphylactic shock, he found capillary congestion with tendency to extravasation of blood into the alveoli, areas of emphysema alternating with atelectasis, edematous fluid, and generalized lymphoid hyperplasia. Dilatation of the right ventricle was observed in the majority of his cases.

In our patient hyperplasia of the lymph glands, particularly of the mesentery, and Peyer's patches were striking. The spleen and thymus were also enlarged. Edema and emphysema of the lungs were also present and on histologic examination areas of emphysema alternating with atelectasis were seen. Dilatation and flabbiness of the right heart were also present. It is obvious that the changes found by us in the organs closely resemble the changes found by Waldbott. We wish to point out, however, that, because of the generalized edema, the edema of the lungs is not as significant as it would be under other circumstances. Other observers have reported hyperplasia of the thymus and other lymphoid organs in sudden death following the administration of drugs.[5]

Because of the similarity of the findings in our cases with those of Waldbott in his cases, we feel that death was due to shock. The fact that a chemical was employed in the injections does not exclude the possibility of a "shock" death. According to Landsteiner and van der Scheer,[6] whole groups of substances—benzylchlorides and acylchlorides—characterized by a certain chemical reactivity have the capacity to produce sensitization.

In a subsequent communication Landsteiner and Jacobs[7] gave further evidence of anaphylaxis induced by chemicals; in experiments with arsphenamine typical anaphylactic shock was produced in a high proportion of the guinea pigs treated. Others observers,[8, 9] have demonstrated that the injection of drugs may produce symptoms identical with those seen after injections of pollen or horse serum into a sensitive individual. Waldbott also observed symptoms of true anaphylactic shock after the intravenous injection of sodium iodide in one case and methenamine-quinine in another. The time interval between two injections may, under certain conditions, enhance the degree of sensitization. Anaphylactic shock depends on the degree of individual sensitivity, the method of administration, the rate of absorption, and a dosage which exceeds the patient's tolerance. Possibly all four factors were responsible for death in our patients. In the first patient sensitization was probably produced by the employment of the intramuscular route for the first two injections. Although neptal in itself is not an antigen, yet, when injected intramuscularly, contact with the local tissues may bring about the formation of a conjugate antigen with the body's own protein, thus sensitizing the individual (Landsteiner). In view of the fact that the intravenous injection in the first patient was given seven to twelve days after the intramuscular injections, we believe it may well have acted as the shocking dose.

Finally, we feel that, in spite of the bad results reported here, neptal or salyrgan or novurit should not be abandoned as a method of treatment for the elimination of edema in nephrosis. We wish to emphasize, however, that, if the intramuscular route is employed, it be used exclusively and not changed subsequently to the intravenous route; the intramuscular injection, because of its contact with the local tissues, may act as the sensitizing dose and the intravenous injection, especially when given after ten or twelve days, may act as the shocking dose. Particularly in children, one should be cautious in the dose employed; it is advisable to start with a small dose and, if no unusual symptoms and signs appear, such as chills, elevation of temperature, malaise, morbilliform rash, headache, vomiting, or convulsive seizures, to increase the dose gradually. These manifestations are danger signals and contraindications to the subsequent administration of the drug.

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# ACUTE NAPHTHA POISONING

## Report of Case in Infant

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SO FAR as we are able to determine, no instance of acute naphtha poisoning in a child has previously been reported.

E. A., a normal, healthy, white boy of thirteen months, playing in the apartment one afternoon while his mother was house cleaning, suddenly began to cough vigorously. His mother rushed to him and found him with an open can of liquid floor polish in his hand. From telltale traces around his mouth and the odor of his breath, it was evident that he had been drinking the fluid. Grabbing him in her arms she rushed to the hospital, arriving within ten minutes of the time of his initial coughing. Within this short period of time, however, he had become extremely cyanotic. His breathing was slow, shallow, and associated with a sonorous sound. The pulse was rapid and weak. The throat was somewhat red, but there was no evidence of any severe burning.

Caffeine sodium benzoate was given immediately as a stimulant, and gastric lavage performed. A fair amount of what appeared to be liquid wax was obtained. The odor of the material was suggestive of kerosene. Following a copious lavage, a half ounce of magnesium sulphate was left in the stomach and the child was placed in the hospital for observation.

The child soon became extremely restless, tossing to and fro upon the bed. Chloral hydrate was given by bowel. There was a moderate amount of thirst, and egg albumen in water was given freely. Within two hours the general condition was greatly improved with an increased volume to the pulse, a lessening of the cyanosis, and an increase in the rate and depth of respiration, although the sonorous respiratory sound persisted. During the following night the temperature rose to 102° F. and the restlessness returned, necessitating further use of sedatives.

By the following morning the child appeared to be in good condition. The cyanosis had disappeared, the pulse was of good quality, and the boy was in excellent spirits. A few scattered moist râles were heard over both lungs.

From this time on, recovery was rapid. At the end of forty-eight hours the temperature subsided to normal. The hoarseness persisted for several days but eventually disappeared. At the end of two weeks

a careful examination, including an examination of the blood, revealed the boy to be in excellent condition with no evidence of his recent trouble.

COMMENT

There is no doubt that the factor in the liquid wax which caused the symptoms described above was naphtha. In answer to a letter of inquiry to the company which manufactures this brand of wax, the following information was received from the general manager.

"Our Liquid Wax is composed of three elements. First, the wax itself is a blend of various waxes. Waxes, as you know, are chemically inert and certainly should not have caused any reaction. In fact, as far as the wax base is concerned, it would seem the result would be just about the same as when we, in our youth, chewed up and inadvertently swallowed some of that very cheap chewing gum which seems to be nothing more than sweetened paraffin wax, except for the fact that our waxes are harder than paraffin and in a more finely divided state.

"Second, the solvent is a petroleum naphtha and this, no doubt, was what caused the acute sickness. We suppose the effect might have been something like drinking kerosene or gasoline.

"Third, a very small amount of coloring matter is used in this wax, said color being an aniline which is a coal-tar product, but this is such a very, very small percentage that it could not even be detected except by fine qualitative analysis in a chemical laboratory and its effect would undoubtedly be nil in this case."

Naphtha is one of the group of hydrocarbons which is obtained by the fractional distillation of petroleum. Other members of this group are petroleum, ether, gasoline, benzine, and kerosene. Poisonous symptoms arise when these substances are inhaled in the form of a vapor or when they are taken by mouth.

Naphtha poisoning through inhalation is not infrequently met with in industry, and the mild form is commonly referred to as a "naphtha jag." Bronchitis or other inflammations of the respiratory tract may arise.[1]

Poison from naphtha taken by mouth is rare and, as has already been mentioned, no account of this type of poisoning in a child can be found in the literature.

In a previous article dealing with poisoning by kerosene,[2] we introduced the idea that prognosis, following the taking of kerosene by mouth, would depend upon two factors: symptoms arising from the kerosene in the stomach itself, and the symptoms which follow the aspiration of the poison into the lung. Waring[3] arrived at the same conclusion through experimental work upon dogs. Naphtha is so closely allied to kerosene that the same factors hold true for both poisonings.

The symptoms which result from ingestion of naphtha are dependent upon the amount of poison swallowed and absorbed. The earliest symptoms are those caused by local irritation of the alimentary tract; a burning sensation in the mouth, throat and stomach, vomiting, thirst, and colicky pains. As the volatile products of the hydrocarbon are absorbed from the stomach, further symptoms arise: shallow respiration, weak pulse, cyanosis, extreme restlessness, and unconsciousness. All of these symptoms, as shown by the case reported, may make their appearance within a few minutes after the poison is swallowed.

The symptoms which result from aspiration of the poison are those of irritation of the respiratory tract: cough, tracheitis, dysphonia, bronchitis, and, in severe cases, bronchopneumonia.

Treatment in naphtha poisoning, as in kerosene poisoning, consists of the removal of the poison as quickly as possible, and attention to complications as they develop. The stomach should be washed out immediately with large amounts of water, and it is advisable to leave a dose of magnesium sulphate in the stomach after the lavage is completed. Stimulants should be used freely if indicated, and sedatives may be necessary to control the restlessness. After the subsidence of the acute and alarming symptoms, special attention should be directed to the lungs, and final prognosis should be withheld until forty-eight hours have elapsed from the time the poison was taken. If at this time the lungs are entirely clear, it may be assumed that the danger is past.

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# CONGENITAL BRONCHOGENIC CYST OF THE MEDIASTINUM

## Report of a Case

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I WISH to present a case of a congenital mediastinal cyst arising from the tracheobronchial tree in an infant.

Reports of cystic tumors of the mediastinum are not uncommon in the literature. One of the rarest examples, however, is that which apparently originates in displaced germs of the tracheobronchial tree. Of this type, Hare found no recorded example in reviewing about 600 mediastinal tumors reported before 1899. Since then, mediastinal cysts of bronchogenic origin have been described in the European journals by Goel, Gold, Mathais, Preuss, Sultan, and Nossen and, in the American publications only by Mixter and Clifford. In addition to its rarity, this case is of interest because the cyst produced a clear-cut clinical picture, and it played a primary part in the cause of death.

S. C., a white female infant, aged seven months and two weeks, was admitted to the Buffalo Children's Hospital, Dec. 31, 1934, for cough, dyspnea, and cyanosis. She died Jan. 5, 1935.

The family history was irrelevant. The present illness began three months before admission, at which time the patient was said to have suffered from bronchial asthma. The attack lasted three weeks. Recovery followed except for a slight cough which persisted. Four days before admission the baby's wheezing cough became accelerated, and her parents noted that she desired to sleep. Feedings were taken poorly because the child was "choked up." She appeared to be continually hungry but was unable to swallow because of "phlegm." Just before entrance to the hospital breathing became rapid, and the child appeared to be definitely worse. There were spells of cyanosis.

Physical examination revealed a well-developed and well-nourished female baby breathing rapidly, laboriously, and noisily. There was distinct dilatation of the alae nasi. A considerable amount of mucus was found in the pharynx. The chest showed slight dullness to percussion at the right apex posteriorly, with numerous coarse râles. The left chest was clear. The heart was not enlarged. The sounds were rapid but of good quality. No murmurs were heard. The abdomen was distended, but no organs or masses were palpable.

During the stay of the child in the hospital, the temperature was elevated and pulse and respiration were accelerated. The temperature varied between 102° and 108° F. (terminally). Cyanosis appeared frequently and was relieved by holding the child in the upright position. Feedings were tolerated poorly; cyanosis occurred at each feeding time. Oxygen therapy brought considerable relief.

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From the Pathological Laboratories of the Buffalo General and Children's Hospitals and the University of Buffalo Medical School, K. Terplan, M.D., Director.

Abstract read at the monthly meeting of the Buffalo Pathological Society, November 14, 1936.

Fig. 1.—Radiogram of chest showing bronchopneumonia of right upper lobe with emphysema of the left lung. There is a distinct shift of the mediastinum to the right.

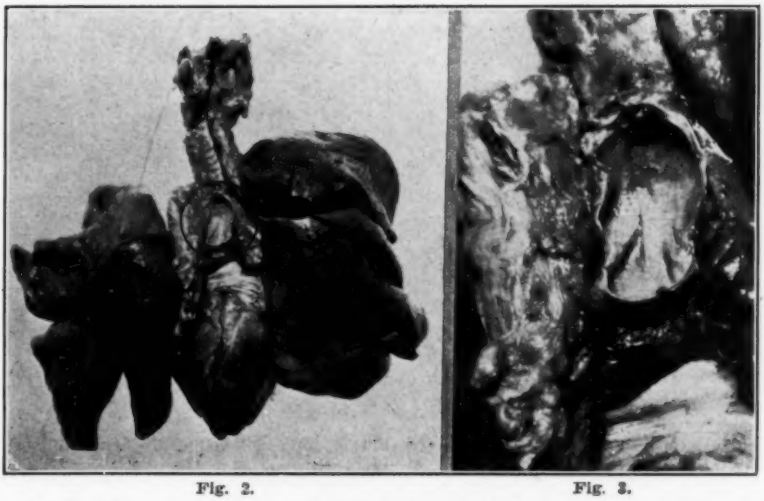

Fig. 2. Fig. 3.

Fig. 2.—Gross view of the cyst (within the circle) showing its relation to the trachea, left major bronchus, and thoracic aorta. The roof of the cyst has been removed.

Fig. 3.—Magnified gross view of cyst showing the thin wall and the rings of the trachea shining through in the superior portion.

X-ray examination of the chest on admission (Fig. 1) showed an area of bronchopneumonia in the right upper lung. The left lung was somewhat emphysematous. The trachea was displaced to the right. On Jan. 2, 1935, the child was given a barium mixture, but no evidence of herniation through the diaphragm was noted.

Fig. 4.

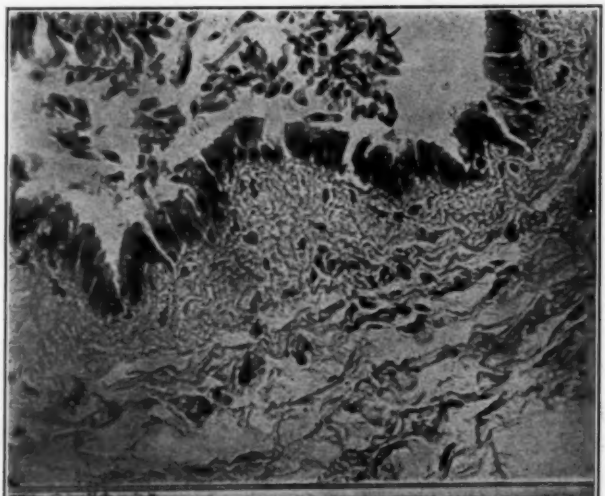

Fig. 5.

Fig. 4.—High power photomicrograph showing high columnar epithelium with basal nuclei and much epithelial desquamation.

Fig. 5.—Section through the wall of the cyst under very low power showing cartilage, glands, vessels, and fibrous tissue.

The urine showed a two-plus albumin with a few pus cells per high power field. The clinical impression was bronchopneumonia.

*Autopsy Report.*—The postmortem examination was performed about four hours after death by Dr. K. Terplan. The anatomic diagnosis was congenital mediastinal

cyst with compression of the trachea and the left major bronchus; diffuse confluent lobular and bronchopneumonia of both lungs; alveolar and interstitial emphysema of the left upper lobe; purulent tracheitis and bronchitis; petechial hemorrhages in pleura and epicardium; distinct anemia of the heart; slight dilatation of the right ventricle; slight atrophy of the thymus; diffuse fatty degeneration of the liver.

*Description of Mediastinal Cyst.*—In the mediastinum a large cherry-sized cyst filled out the upper angle between the trachea and the left major bronchus. It measured 2 × 1.2 cm. in diameter. It occupied the space between these structures and the esophagus. The main portion lay on the posterior surface of the left major bronchus and extended on the left posterolateral surface for a distance of 1.5 cm. above the bifurcation. Medially it bordered on the carina. The lateral edge projected about 0.5 cm. beyond the trachea. The inferior border was adjacent to the inferior tracheobronchial lymph nodes. On further examination the cyst was found to be adherent on its lateral wall to the arch of the aorta. The left vagus nerve was incorporated at this point (Figs. 2 and 3).

The wall was thin and translucent. In thickness it approximated a sheet of foolscap. The contents comprised a saliva-like white mucoid material. The lining of the cyst was somewhat whitish in color. No hemorrhages were seen. At the superior pole, within the wall, was a firm white plaque, which had the consistency of cartilage and measured 0.5 cm. in diameter. The rings of the trachea and bronchus showed through the cyst wall. The cyst was made up of one large locule with two very small locules at its superior pole within the larger portion.

When the respiratory tubes were opened, it was observed that the cyst caused an inward bulging of the trachea at its junction with the left major bronchus and by this mechanism almost completely occluded this opening in the trachea.

The cyst, together with the adjacent trachea and left bronchus, was removed and fixed in formaldehyde for microscopic examination. Paraffin sections were cut and stained by hematoxylin and eosin, van Gieson, and Weigert elastic tissue stains.

Histologically, the cyst proved to be of bronchogenic origin. Its structure was multilocular at the superior pole. For the most part, the lining was not preserved. Where present, the epithelium was columnar and in some places cuboidal in character. The cells showed a mucous border. Some possessed cilia. The nuclei were basal in position and round. In certain areas the epithelial cells were flattened, apparently from pressure exerted by the contained fluid. Desquamation of the lining was prominent.

The wall contained cartilage, glands, connective tissue, and smooth muscle fibers. In addition there were numerous nerves and small vessels surrounded by a slight infiltration of neutrophilic leucocytes. The cartilage was distributed in a circular manner as isolated elliptical plaques. The borders of these plaques were smooth. The character of the cartilage was embryonal with many nuclei. The connective tissue fibers were densely packed. The glands were arranged singly and in groups. Their epithelium consisted of a single layer of cuboidal cells with central dark nuclei. The lumina contained a basic staining secretion (Figs. 4 and 5).

The wall of the left bronchus and the wall of the cyst were intimately connected with each other. In one area the cyst protruded into the wall of the bronchus. No communication, however, could be demonstrated between the lumen of the cyst and the lumen of the bronchus in sections examined.

## DISCUSSION

In a case of a bronchogenic cyst of the mediastinum it is extremely interesting to speculate as to the embryologic accident that caused the formation of this rare structure.

Mathais stated that "genetically there are two conditions to be considered, that is, displacement of a hollow, pipelike organ developing into a cyst or displacement of a flat plaquelike piece from the bronchial tree." He stated further that "because of the mechanical force inherent in embryonal germs, flat pieces of tissues have a tendency to grow into ball-shaped bodies, as for example, cysts which develop after implantation of germs of ovarian cystomas in the abdominal wall."

The earliest primordium of the respiratory organs as described in a 2.5 mm. embryo is the so-called laryngotracheal groove, running lengthwise in the floor of the foregut immediately caudal to the pharyngeal pouches. This entodermal groove is destined to become the larynx, trachea, and esophagus; its rounded caudal end is the anlage of the unpaired bronchi and lungs. Along the sides of the respiratory primordium are two longitudinal furrows; they grow in deeper and deeper until the esophagus is finally separated from the laryngeal groove. At about this stage or in the 4 mm. embryo the primary bronchi begin to form. Probably during this cutting-off process by the before mentioned lateral grooves, a plaque may be abnormally separated which represents the possible anlage of a mediastinal bronchogenic cyst.

The size of the cyst in our patient at birth and the rate of development in size is problematic. From a review of the clinical history it is reasonable to assume that the cyst began to produce symptoms when the child was about four months old. At this time she suffered an attack of "bronchial asthma" which lasted for a period of three weeks. This attack was, in all probability, due to partial occlusion of the bronchial orifice by pressure of the cyst together with inflammation. How much of a part was played in this episode by pressure on the left vagus nerve by the cyst or the mechanism whereby an asthmatic attack may be initiated from such vagus pressure is merely a matter of conjecture, but it is, however, a factor to be considered.

The onset of the terminal illness, four days before admission to the hospital, was undoubtedly an acute upper respiratory infection which progressed into tracheitis and bronchitis. The cyst had now become large enough to produce definite occlusion of the orifice of the left bronchus. In addition, the superimposed inflammation in the bronchus, as the result of infection, aggravated the obliteration. The marked emphysema of the left lung with displacement of the trachea to the right, detected during the life of the patient by roentgen x-ray, points to subtotal obstruction of the left major bronchus. Lobular pneumonia developed and progressed rapidly.

Change in the child's position during acute attacks of dyspnea and cyanosis apparently relieved the pressure of the cyst on the bronchus sufficiently to allow enough air to pass through to relieve these attacks.

The cyst was too small to give pathognomonic physical signs or positive radiographic findings.

In comparing this case with those of other bronchogenic cysts that have been reported in the available literature, we find that two of the authors have found the cyst in the pericardium. Mathais and Goel described these cases, and in each the patient died suddenly of occlusion of the pulmonary artery.

Sultan and Preuss each reported bronchogenic cysts arising from the anterior wall of the left major bronchus and attached by small pedicles. In both instances these were removed surgically with success. In Nossen's case, the cyst was in contact with the pericardial sac, but was at its origin attached to the major bronchus.

Gold has described four cases of mediastinal bronchogenic cysts in children. Three of these were found incidentally at autopsy after the infants had died of diseases not related to the cysts. In the other case the cyst played a primary part in the cause of death. The child was seven months old and clinically had dyspnea, cough, and an obstructive type of breathing, with physical signs of emphysema. At autopsy a bronchogenic cyst was found in the mediastinum at the bifurcation of the trachea, more to the right than to the left. It caused obstruction of both major bronchi. In addition, there was a bilateral bronchopneumonia.

The case described by Mixter and Clifford closely resembles the case that I have described. The cyst occurred in an eight-month-old infant and by pressure occluded the left major bronchus. The child died of a lobular pneumonia that was directly caused by pressure closing the main passage to the left lung.

## SUMMARY

The clinical and postmortem findings of a case of a bronchogenic cyst of the mediastium in a female infant seven months and two weeks old, are presented. Pathologically the cyst caused distinct compression stenosis of the left major bronchus at its orifice. As a result of the occlusion the child showed difficulty in breathing and developed pulmonary emphysema. Death was caused by lobular pneumonia.

This case was on the service of Dr. H. Lohnes.

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# ABSCESS OF THE EPIGLOTTIS IN AN INFANT

## Case Report

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ABSCESS of the epiglottis in children is an unusual condition. The literature appears to be lacking in case descriptions. In adults the condition is more frequently encountered but surprisingly little descriptive writing is to be found regarding it. Specialists in diseases of the nose and throat who have had wide experience ordinarily see one or two cases in adults in a lifetime. Four adult cases of this kind have been observed at the Graduate Hospital of the University of Pennsylvania during the past ten years.[1]

Cases in adults usually occur as a complication of acute pharyngitis, often are directly traceable to abscess of the lingual tonsil.[2] Howard[3] reported three cases in adults, two of which occurred as a complication of scarlet fever.

Seitz[4] reported a case of great swelling of the epiglottis in a fourteen-month-old child but without abscess formation.

Theisen[5] reported an unusual swelling of the epiglottis in a boy, aged twelve, necessitating tracheotomy, but abscess formation was not noted.

It is probable that the condition occurs more frequently in children than is supposed, but remains undiagnosed.

The following case is of interest because of its unusual character and the excellent response to direct treatment.

### REPORT OF CASE

A. B., a colored, male infant, eleven months old, was admitted to the pediatric department of the Philadelphia General Hospital, Aug. 29, 1936. Two days prior, the child had developed a moderate fever; he had been fretful, had vomited; he coughed and breathed with some difficulty.

Past and family histories were not significant. Birth, which occurred at the Philadelphia General Hospital, was normal; feeding and general progress had been uneventful; his state of nutrition was relatively good.

He appeared acutely ill on admission. His temperature was 101.4° F. He breathed rapidly (rate 40 per minute) but with some difficulty. He coughed frequently and at times in short paroxysms.

Both nares discharged sticky mucopus which descended over the posterior surface of the pharynx. The pharynx was highly inflamed and the tonsillar tissues swollen and injected.

There was slight indrawing in both suprasternal and supraclavicular spaces.

Breath sounds were harsh and accompanied by coarse rhonci. Signs were present of a small area of consolidation extending from the hilum along the course of the left bronchus.

The heart rate was rapid (pulse rate 120), but no cardiac lesion was detected.

Blood count: White cells, 21,500. Differential; polymorphonuclear, 71 per cent, lymphocytes, 25 per cent, monocytes, 4 per cent. Urine negative. Kahn reaction, negative. Blood calcium, 9.7. Blood phosphorus, 5.3. Mantoux test, negative in both dilutions Mulford P.P.D. Throat cultures, positive for *Bacillus influenzae, Staphylococcus aureus, Streptococcus hemolyticus,* and *Streptococcus viridans,* negative for Klebs-Löffler bacillae.

A provisional diagnosis was made of acute upper respiratory tract infection, acute laryngotracheitis with edema, and acute bronchopneumonia. Request for consultation was made to the bronchoscopic department. It was believed that tracheotomy would be a necessary procedure.

In the following two days (August 30 and 31) the child's condition improved and he breathed with less difficulty.

X-ray report by Dr. Herman Ostrum was as follows:

"Retrotracheal and retropharyngeal spaces normal. No displacement of pharynx, larynx, or trachea. Anteriorly, just below the mandible in the region of the cartilages

Fig. 1.—View of the swollen epiglottis which contained pus.

of the larynx, there is a soft-tissue, irregular, dense shadow, extending well forward. No evidence of extension into the larynx or trachea. This swelling is probably due to infection."

On the following day (September 1) the condition again became critical. Respiratory difficulty progressively increased. Stridor was present in both expiratory and inspiratory phases. Retraction was marked in suprasternal and supraclavicular spaces and present in all intercostal spaces. Perioral cyanosis increased. Vocal sounds disappeared, but a paroxysmal cough persisted.

The child was given direct laryngoscopic examination by Dr. William Moore, the bronchoscopist. An intensely swollen and inflamed epiglottis was visualized. The pillow-like swelling was restricted to the anterior surface of the epiglottis and inclined somewhat to the left. The larynx, although good vision was obstructed by the bulging epiglottis, was believed to be neither edematous nor inflamed to a dangerous degree.

The epiglottis was incised by Dr. Moore and pus evacuated. A culture of the pus was taken but was mislaid before laboratory examination could be made. It is probable that responsibility for the infection may be placed on *Streptococcus viridans*

or *Streptococcus hemolyticus*, or both, which were demonstrated in the culture previously obtained from the throat.

Temporary relief from respiratory distress was followed in a few hours by increased embarrassment. A croup tent was ineffectual in affording relief but the child improved when placed in an oxygen chamber. The profuse mucopurulent discharge which descended from the nasopharynx was removed intermittently by nasal suction. Deglutition was difficult and salt and fluid balance was maintained by hypodermoclysis.

The area of pneumonia to the left of the hilum previously noted assumed larger proportions one week after operation. This was ascribed to aspiration of purulent exudate. A transfusion of 60 c.c. of blood was given, September 14, by indirect method.

Impairment of ability to swallow continued beyond the period of respiratory difficulty.

The report of the x-ray examination of September 15 by Dr. Herman Ostrum stated: "There is considerable widening of the retrotracheal space. The upper portion of trachea and larynx are displaced considerably forward and there is widening and straightening of the superior mediastinum. There is evidently infection or pus formation present in the retrotracheal and retropharyngeal space with extension downward into the superior mediastinum."

The child had a normal temperature at this time and the swelling described was believed to be due to postinfectious tissue swelling rather than pus formation. No operation was attempted and the retropharyngeal and retrotracheal swelling slowly subsided.

The child's convalescence was further complicated by cross-infection with bacillary dysentery and it was not until Oct. 17, 1936 (one and one-half months from admission), that he was discharged from the hospital apparently in good condition. He was brought to the clinic for examination January, 1937, and has had no recurrence.

## SUMMARY

A case of abscess of the epiglottis in a child is recorded. This is not a common occurrence in children but probably is present more frequently than is suspected in cases with acute infections of the pharynx.

The necessity for direct laryngoscopic examination and the value of direct treatment is demonstrated.

The superiority of the oxygen chamber over treatment with croup tent was evident in this case.

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# THROMBOCYTOPENIC PURPURA HEMORRHAGICA

## Two Cases Treated With Parathyroid Hormone and Calcium Gluconate

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IN 1932 Lowenburg and Ginsburg[1] reported a case of induced hypercalcemia in a child afflicted with a purpura of the thrombocytopenic type. Through an error the child received one ampule (100 units of parathormone) instead of 1 c.c. (20 units), daily for six days, before the mistake was corrected. It was noted that coincident with the appearance of the toxic signs of the acute hypercalcemia there was a diminution in the bleeding.

A practical application of this accidentally discovered fact was made by the same authors four years later. Another case of purpura of the same type was under treatment with snake venom and other modes of therapy but the bleeding was not controlled. Lowenburg and Ginsburg[2] recalled their previous experience and parathyroid extract was given to this second case. The response was dramatic, with prompt cessation of the bleeding, rapid rise in the platelet count, and steady increase in the serum calcium and phosphorus.

In September, 1936, we received a patient on the Clinical Service at Children's Hospital with purpura hemorrhagica, and one of us (Edelman) treated a case in private practice with the same diagnosis. Our therapy was similar to that used in the two cases mentioned above. We wish to record our results.

Case 1.—S. W., a white female, aged three years, was brought to the emergency room of the hospital one evening because her mother had noticed several red purple blotches on her body. The mother stated that three days previous the child had had a rash on her face and neck which was quite different in character from the skin lesions in the presenting complaint. The morning before being brought to the hospital the child had a watery diarrhea but there was no history of melena or hematuria. About eight o'clock in the evening the mother noticed the purpuric spots and brought the child to the hospital.

The birth history, developmental history, and past history were all quite normal. No history of a hemorrhagic diathesis in the family could be elicited.

The only significant findings on physical examination were those of the purpura. Several areas were found in the parietal region of the scalp, varying in size from that of a cherry to a pea, that appeared to be hematomas. The forehead and neck had several, red purple, ecchymotic areas. No evidence of bleeding was found in the eyes or nose. The gum tissues showed evidence of hemorrhage, several hematomas were seen in the tongue and there were ecchymoses beneath the mucous membrane

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of the cheeks and oropharynx. The skin of the chest and abdomen was covered with numerous purpuric spots as were all four extremities. The spleen was barely palpable. The remainder of the examination showed no pathology.

*Laboratory findings* on admission included hemoglobin, 90 (Dare); red blood cells, 4,360,000; white blood cells, 13,050; polymorphonuclears, 92 per cent; lymphocytes, 7 per cent; monocytes, 1 per cent. The temperature was 99.2° F.; pulse, 120; respirations, 22. Urinalysis was negative, including the benzidine test for blood.

On the second hospital day the patient began to have epistaxis which was stopped with difficulty with nasal packs of adrenalin. On the third hospital day the epistaxis had become almost a continuous oozing and the interne ordered one dram of ceanothin which had no apparent effect in controlling the bleeding. Three hours later 40 units of parathormone were given intramuscularly along with 10 c.c. of calcium gluconate. Five grains of calcium gluconate were then given by mouth. Several hours later the nasal oozing stopped and no further evidence of active bleeding was seen anywhere in the child during the remainder of the hospitalization. On the fourth day 80 grains of calcium gluconate were given by mouth and one injection of 60 units of parathormone. On the fifth hospital day the patient was given 40 units of parathormone intramuscularly and 80 grains of calcium gluconate by mouth. For the remainder of the hospital stay the patient received as her only medication 80 grains of calcium gluconate daily. Two days after the administration of the last dose of parathormone the purpuric spots turned brown and lost their livid purple appearance. They gradually receded and disappeared.

COMPLETE LABORATORY STUDY

| | PLATELET COUNT | COAGULATING TIME (MIN.) | BLEEDING TIME (MIN.) | SERUM CALCIUM (MG. %) | SERUM PHOSPHORUS (MG. %) | PARATHYROID (UNITS) |
|---|---|---|---|---|---|---|
| Sept. 24 | 40,000 | | | | | |
| 25 | | 2 | over 20 | 8.5 | 1.8 | 40 |
| 26 | | | | | | 60 |
| 27 | | | | 8.8 | 5.2 | 40 |
| 28 | 100,000 | 8 | 5½ | | | |
| 29 | 80,000 | | | 9.4 | 4.8 | |
| 30 | 100,000 | | | | | |
| Oct. 1 | 140,000 | | | | | |
| 2 | 200,000 | | | | | |
| 3 | 380,000 | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | 390,000 | | | | | |
| Wassermann test, negative | | September 25 little or no clot retraction at the end of twenty-four hours. | | | | |
| Repeated urinalyses, negative | | September 25 fragility test showed normal fragility. | | | | |

Three weeks later the patient was seen in the dispensary. She had had no further bleeding. Platelet count was 410,000 and calcium was 8.7 mg. Six weeks after admission the patient was again seen in the dispensary. Her coagulation time was 3 minutes; bleeding time, 3 minutes; platelet count, 230,000; calcium, 10.3; and phosphorus, 4.4.

CASE 2.—B. D., a white female, aged four years, was brought to the hospital because of severe epistaxis that could not be controlled by the ordinary methods.

Three weeks prior to admission the patient had a skin rash accompanied by the constitutional symptoms of angina and emesis, fever, and malaise. In retrospect

it is believed that this was scarlet fever. At 5 A.M. on Jan. 12, 1937, the girl developed a severe nosebleed that was not controlled by the ordinary methods. The child refused to eat, was irritable, and complained of abdominal pain. The epistaxis continued all day, and in the evening she was brought to the hospital.

The past history was nonessential except for the acute illness three weeks before, which is mentioned above. There was no history of a bleeding diathesis in the family.

*Physical Examination.*—The child had a lemon yellow tint to the skin but was not jaundiced. The main features of the examination were the purpuric manifestations. She was bleeding freely from both nares but there was no evidence of hemorrhage in the gums, tongue, or oropharynx. There was evidence of hemorrhage behind the left membrana tympani. Multiple pinpoint purpuric spots were seen over the lower abdomen and both lower extremities. The skin was desquamated at the finger tips. The spleen was palpable as it was in the first case. The liver was not palpable. Except for a congenital heart lesion no other pathologic findings were recorded on the physical examination.

Laboratory findings on admission included red blood cells, 4,310,000; white blood cells, 20,400; polymorphonuclears, 72 per cent; lymphocytes, 27 per cent; monocytes, 1 per cent. The temperature was 101.2° F.; pulse, 124; respirations, 22. The urine was negative.

*Course in the Hospital.*—January 12, the patient was given 5 c.c. fibrinogen immediately and 2 c.c. additional were given six hours later with no noticeable effect on the bleeding.

On January 13 epistaxis continued. Parathyroid hormone, 50 units, was given at 5:00 P.M.

On January 14 epistaxis was still present and large ecchymoses appeared at the site of the hypodermic injections. Purpuric spots on the extremities were larger. Parathyroid hormone, 50 units, was given at 12:30 A.M., and 50 units at 8:00 A.M. Calcium gluconate, 15 grains twice daily, was begun and continued throughout the course of treatment.

Epistaxis was only slight in amount on January 15. Parathyroid hormone, 50 units, was administered at 10:00 A.M.

On January 16 bleeding stopped entirely. There was no further epistaxis and ecchymoses did not appear after hypodermic injections. The patient was given parathyroid hormone, 50 units, at 11:00 A.M.

COMPLETE LABORATORY STUDY

| | PLATELET COUNT | R.B.C. | W.B.C. | CALCIUM (%) | BLEEDING TIME (MIN.) | COAGULATING TIME (MIN.) |
|---|---|---|---|---|---|---|
| Jan. 13 | 15,000 | | | | 8 | 7 |
| 14 | | | | 9.7 | | |
| 15 | | | | | | |
| 16 | 1,000 | 2,630,000 | 13,000 | 10.0 | | |
| 17 | | | | | | |
| 18 | | | | | | |
| 19 | 4,000 | 2,430,000 | 15,100 | | | |
| 20 | | | | 11.5 | | |
| 25 | 55,000 | 3,420,000 | 11,200 | | | |
| 29 | 126,000 | 3,240,000 | 8,600 | | | |
| Feb. 5 | 196,000 | 4,010,000 | 7,100 | 11.5 | | |
| 26 | 240,000 | 4,200,000 | 12,000 | | | |

Wassermann test, negative. Blood culture negative.

Widal test, negative. Throat smear, Staphylococcus and Streptococcus, positive.

## DISCUSSION

The hemorrhagic conditions described as purpura can be broadly classified into two main groups, the nonthrombocytopenic and the thrombocytopenic types. The latter is further subdivided into those that are secondary to some known factor and those that are idiopathic in origin.

The cases that we have recorded belong to the thrombocytopenic type. The first case is idiopathic in origin while the second one followed one of the acute exanthemas.

The therapy of those purpuric states with a normal platelet count was eminently unsuccessful until the use of snake venom was introduced by Taylor, Peck, and their associates.[3, 4, 5, 6] The successful use of snake venom and antivenin was not paralleled in the treatment of the thrombocytopenic purpuras.

The list of therapeutic measures used in the treatment of purpura hemorrhagica is imposing and is probably an index to the lack of specificity of any one of them. Blood transfusions have long been used because they seem to increase the coagulation of the blood and because they are necessary to replace the blood elements that have been lost through hemorrhage. Whole blood given intramuscularly and intraperitoneally is also valuable. All ordinary hemostatic measures are used with fair success and such coagulants as thromboplastin have been used both subcutaneously and topically. High protein diet, liver therapy, ultraviolet light, and a high calcium-viosterol regime are a few of the other modes of treatment. Recently the intravenous use of ascorbic acid has been advanced on the postulate that vitamin C is a factor in the manufacture of the matrix of the capillary walls. Splenectomy has yielded consistently good results when all else has failed.

We add to this imposing armamentarium, the empirical use of large doses of parathyroid hormone and calcium gluconate. There is no good theoretic basis to advance other than that perhaps the parathormone makes the blood calcium more available for the clotting cycle as postulated by Howell. In our two cases we had a prompt cessation of the purpuric manifestations, the blood calcium and the platelet count increased *pari passu*. Lowenburg and Ginsburg reported the same findings in their two cases. We believe the use of parathormone in the bleeding diatheses warrants further clinical trial and investigation.

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# HEMORRHAGE FROM MECKEL'S DIVERTICULUM

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IN 1701 Ruysch first described the existence of an anatomic structure which later was described more fully by Meckel in 1812, and has since been called by his name. According to Arey, in the early embryo of 1.5 mm. to 2 mm., with the development of the fore- and hind-gut, the entodermal vesicle is divided into a dorsal intestine and a ventral yolk sac, with a narrowed portion between. With the growth of the embryo and the yolk sac, the connecting portion does not increase much in size, and eventually becomes a slender yolk stalk. This yolk stalk later becomes a slender thread extending from the junction of the fore- and hind-gut to the yolk sac, or umbilical vesicle. It loses its attachment to the gut in the 7 mm. embryo. A blind pocket may persist at the point of its union with the intestine. This is known as Meckel's diverticulum. The blind end of this pouch may remain adherent to the umbilicus, or may separate and lie free in the abdominal cavity. The lumen of the pouch is continuous with that of the ileum, about 80 cm. above the ileocecal valve.

We feel that hemorrhage from such diverticulum is of sufficient rarity to warrant this report of the following two cases.

Case 1.—M. U., a male, 6 years old, of Polish extraction, was first seen Jan. 25, 1937.

About one year previous the child was taken to a physician because of a small amount of dark blood noticed in the stool. This was thought to originate in a rectal fissure, and did not recur. Uncomplicated chickenpox occurred three weeks before admission. Four days previous to admission the mother noticed some dark red blood in the stool. The child showed no other symptoms, and had no increase in the number of stools. Two days before admission the blood recurred in the stool and was more plentiful. The child still showed no other untoward symptoms. The day preceding admission he had no stools and seemed well. On the day of admission he had a large stool in the morning which consisted almost entirely of dark blood. He showed no evidence of acute illness until noon, when he became pale and weak. He refused luncheon, vomited once during the afternoon, and became rapidly paler and weaker, although he had no further stools. He had no pain at any time. The child was seen by the family physician who referred him to the hospital.

*Physical Examination.*—On admission at 5 P.M. on January 25, the child appeared dangerously ill. The facies were drawn and anxious, and the skin, lips, and mucous membranes were pale and dry. The abdomen was flat, soft, not tender, and no masses or rigidity could be palpated. Rectal examination was negative except for the presence of considerable old blood. The temperature was 101° F.; the pulse, 130; and the respirations, 22. The remainder of the physical examination was entirely negative.

*Laboratory Findings.*—Hemoglobin, 25 per cent (Sahli); red blood cells, 2,270,000; white blood cells, 23,000; polymorphonuclears, 82 per cent; lymphocytes, 18 per cent; no abnormal white cells; red cells showed poikilocytosis and anisocytosis,

but no normoblasts. Platelets 184,000; normal clot retraction; coagulation time, three and one-half minutes. Bleeding time was not increased. Blood was type 2 Morse. The urine was normal except for high specific gravity and 3 plus acetone.

*Clinical Course.*—The child was given a blood transfusion at once, receiving 360 c.c. of whole blood by direct method. A low enema yielded nothing but clotted, and partially destroyed blood. The laboratory reported that this stool showed red blood cells in all stages of disintegration, with a few apparently normal red cells. The stool was negative for ova and parasites.

The next morning the color was improved, and the hemoglobin was 39 per cent (Sahli) with red blood cells numbering 2,850,000. Temperature was 99°; pulse, 105; respiration, 18. An enema yielded a large amount of old blood. There was no spontaneous stool. He received 400 c.c. of whole blood by direct transfusion.

That evening he had a large, dark red, liquid stool and again showed signs of shock. It was decided not to postpone operation any longer, as he was suspected of having fresh bleeding into the bowel from a persistent Meckel's diverticulum.

At 1 A.M. on Jan. 27, 1937, the abdomen was opened. The peritoneal cavity contained a small amount of clear fluid. The whole colon appeared relaxed and atonic and was distended with dark blood, which showed through its wall. About 15 inches proximal to the ileocecal valve, was found a large diverticulum about 4 inches long, and of the same diameter as the adjacent ileum. The diverticulum was clamped, ligated, and removed. Its stump was cauterized and inverted with a purse-string suture.

The temperature dropped to normal twenty-four hours after operation and the postoperative course was uneventful. The hemoglobin rose to 64 per cent (Sahli) with a red blood count of 4,400,000 on the ninth day. The child was discharged in good condition on the eleventh day, and has remained well since.

*Pathologic Report by Dr. Margaret Loder.*—Macroscopically the specimen consisted of a diverticulum measuring 50 to 60 mm. in length. Approximately 30 mm. from the closed end, the mucosa showed an ulcerated area 8 to 10 mm. in diameter, with an increase of fibrous tissue in the wall, and some constriction. Definite bleeding points appeared in the floor of the ulcer. The mucosa around the edges of the ulcer appeared congested.

Microscopically the sections showed a definite ulceration of the mucosa, with an increase of adult fibrous tissue in the submucosa and muscularis. Leucocytic infiltration was present at the base of the ulcer, perivascular and moderate diffuse infiltration in the stroma of the submucosa, and infiltration to a lesser extent in the muscularis. The mucosa and lining epithelium were typical of that found in the adjacent ileum. An area in which the surface glands were lined by a large clear cell, usually found in the peptic glands of the stomach, was found near the edge of the ulcer in the sections examined.

*Pathologic Diagnosis.*—Bleeding ulcer in a persistent Meckel's diverticulum.

CASE 2.—MacM., a male two years of age, of American parentage.

*Present Illness.*—On Jan. 28, 1937, the child was given Ex-lax because of constipation. On January 29 he had four bowel movements, three of which contained blood. The father thought that the blood was "somewhat bright." The next day the child had only one stool which contained blood. His appetite remained fairly normal and he had no symptoms that attracted the parents' notice except for one emesis. He had no stools on January 31, nor on February 1. The child suddenly became very weak, pale, and languid toward evening of February 1. He was admitted to the hospital at 5 P.M.

*Physical Examination.*—Temperature was 100° F.; pulse, 140; respiration, 30. Color was very pale; the child, very quiet and apathetic; lips, skin, and mucous membranes were very pale and dry. Blowing systolic murmur was heard at the

cardiac apex. Abdomen was flat, soft, not tender, and showed no palpable mass or rigidity. Rectal examination was negative except for the presence of old blood in large amounts. The remainder of the physical examination was irrelevant.

*Laboratory Findings.*—Hemoglobin, 33 per cent (Sahli); red blood cells, 2,300,000; white blood cells, 10,200; polymorphonuclears, 39 per cent; lymphocytes, 51 per cent; normoblasts, 10 per cent. Blood was type 4 Morse. The urine showed albumin plus, and occasional hyalin casts.

*Clinical Course.*—One hundred forty cubic centimeters of whole blood was given by direct transfusion on admission, and 150 c.c. the next morning. A diagnosis of hemorrhage from a persistent Meckel's diverticulum was made, and the abdomen was opened at 4 P.M. on February 2. A small diverticulum, about the size of the distal phalanx of the thumb, was found about 10 inches proximal to the ileocecal valve. This was clamped, ligated, removed, and the base cauterized and inverted by a purse-string suture. The diverticulum was opened in the operating room and clotted blood found in its lumen. The appendix, which appeared normal, was removed in the usual manner.

The immediate postoperative course was uneventful, and the hemoglobin rose to 45 per cent (Sahli) in twenty-four hours. On the third postoperative day he seemed restless, refused food, vomited once, and the temperature rose to 102.6°. Examination showed an acute nasopharyngitis. On the fourth day postoperative he developed loose green stools with mucus but no blood. This condition persisted for four days with temperature fluctuating between 100 and 102°, and gradually falling to normal on the eighth postoperative day. He was discharged on February 16, fourteen days following operation, apparently in good condition. Through some oversight, the blood count was not repeated before discharge.

*Pathologic Report by Dr. Loder.*—Macroscopically the specimens submitted consisted of: (a) A short, narrow, diverticulum measuring 20 mm. in length. The specimen had been sectioned lengthwise, and the contents lost. The mucosa was smooth throughout. The wall appeared to be moderately thickened. There was no evidence of acute inflammation. (b) An appendix showing some hyperplasia of the lymphoid tissue, and an otherwise grossly normal wall. Dark feces was found in the lumen.

Microscopically the sections from the diverticulum showed a mucosa, lined by epithelium similar to that of the adjacent ileum. The surface epithelium of the sections examined appeared intact. There was an increase of fibrous tissue in the submucosa, muscularis, and subserosa. Perivascular and moderately diffuse infiltration, consisting of small round cells, plasma cells, and a few polynuclear leucocytes, was found in the stroma of the mucosa, submucosa, muscularis, and subserosa.

Sections from the appendix showed perivascular infiltration in the outer muscular, and subserous layers. The lymphoid tissue was hyperplastic.

*Diagnosis.*—Chronic Meckel's diverticulitis. Mild chronic appendicitis.

## COMMENT

We feel that these cases should be reported because they are typical of one of the true pediatric emergencies. Without adequate treatment these children might well be lost, as has been reported by Callender[1] and Taylor.[2] The first case reported was certainly in a very critical condition when admitted, and a guarded prognosis was given. It was considered poor surgical judgment to operate on this child immediately upon admission, due to the existing condition of shock. Apparently this child lost his blood very rapidly, as is indicated by the complete absence of any signs of blood regeneration in the blood smear.

The second case reported was in better physical condition upon admission. He had apparently lost less blood, and had probably lost it more slowly as indicated by the normoblasts seen in the blood smear.

There are certain similarities in these two cases which may be considered as typical of cases of severe hemorrhage from a persistent Meckel's diverticulum. These might be enumerated as follows:

1. The onset is often insidious, and usually without subjective symptoms. Mason and Graham[3] noted that the bleeding may extend intermittently over a period of months or years, if not severe.

2. Neither of these cases showed diarrhea or tenesmus. Chesterman[4] remarks that diarrhea is unusual in these cases, and occurs only with severe, rapid hemorrhage. We believe that this is due to the fact that the bleeding occurs far enough above the ileocecal valve, so that the blood enters the colon slowly. Also the walls of the colon lose their tonicity, probably as a result of the increasing blood loss. This lack of tone probably increases as the loss of blood continues, so that our two cases had no spontaneous stools just before admission, in spite of the presence of considerable old blood in the colon and rectum.

3. The blood in the stools was mostly old but some fresh blood cells were found microscopically. This localizes the bleeding point above the lower bowel but not as high as the duodenum.

4. In our cases there was no evidence of any appreciable peritoneal irritation, as indicated by the absence of pain, tenderness, or rigidity. This was helpful in ruling out duodenal ulcer and appendicitis. Cobb[5] in reporting a series of 100 cases of peptic ulcer in Meckel's diverticulum, found that pain was a symptom in 80 per cent. Usually this was vague abdominal pain, often of a colicky nature referred to the umbilicus, and only rarely simulating the discomfort of duodenal ulcer. It is interesting to note that 55 of these cases eventually perforated.

5. These children show clinical and laboratory evidence of a much more rapid and severe loss of blood than is indicated by the amount passed in the stool. This is helpful in ruling out bleeding from lesions of the lower bowel such a papillomata, colonic ulcers, or hemorrhoids.

6. These children did not vomit blood as might happen in gastric or duodenal ulcer hemorrhage.

7. They remained relatively well for a considerable period after the bleeding started. This resulted in a delay in medical attention. When a certain level of blood loss was reached, they suddenly became dangerously ill, and prompt action was needed.

8. The response to surgical removal was prompt and absolute.

The cases are interesting in that they illustrate two different pathologic types of bleeding Meckel's diverticulum. The first case showed a definite ulceration to explain the hemorrhage, whereas the pathologist was unable to demonstrate any source of the bleeding in the second case, although clotted blood was definitely present in the diverticulum at the

time of operation. This latter condition has been reported frequently in the literature. Chesterman[4] suggests that the hemorrhage in these cases must be due to recurrent inflammation of a hemorrhagic nature, or possibly to acute microscopic ulceration. Farr and Penke[6] give a more plausible explanation by suggesting that the hemorrhage is due to ulceration in the wall of the adjacent ileum. A confirmation of this opinion is found in Cobb's[5] analysis of 45 cases in which the location of the ulcer was described. He found that in 11 per cent, the ulceration occurred outside of the diverticulum, in the wall of the adjacent ileum.

It is also interesting to note that our first case showed cells in the mucosa near the margin of the ulcer, which resembled cells found normally in gastric mucosa. Kaufmann[7] states that islands of gastric mucosa, complete gastric mucosa, or even pancreatic tissues, may be found in the mucosa of Meckel's diverticula. Greenwald[8] reports that 22 in a series of 23 cases of ulceration of Meckel's diverticulum, examined microscopically, showed the presence of gastric mucosa.

It has been stated that it is probably impossible to demonstrate Meckel's diverticulum by roentgenogram. This was discussed in a conference at the Massachusetts General Hospital in March, 1936,[9] and also by Golden.[10] Caffey[11] informs me that he believes the reason to be due to the relationship existing between the opening of the diverticulum, and the plane of the ileum.

We believe that it is highly probable that many cases of bleeding Meckel's diverticula are falsely diagnosed as duodenal ulcers, papillomata, internal hemorrhoids, and other conditions, when the blood loss is not severe or long continued. In the past two years 28 cases of Meckel's diverticulum with hemorrhage have been reported in the American literature by several authors.[6, 9, 12, 13, 14, 15, 16]

This condition should be kept in mind whenever blood is found in the stool which cannot be explained by an obvious cause.

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# THE TECHNIC OF INTRAVENOUS TRANSFUSION OF BLOOD IN NEWBORN INFANTS

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FOR most purposes the safest and most effective transfusion is the intravenous administration of whole blood.[1, 2] In certain conditions other methods may be considered more suitable, but the usual reason for their use in newborn infants is the difficulty of the intravenous administration. This paper is concerned with the technic of administration, so that only brief consideration will be given to the therapeutic value of the various methods.

In the subcutaneous or intramuscular injection very little blood as such is absorbed into the circulation, so that it can hardly be classed as a transfusion. It is a method of administering protein and iron, and as such has a therapeutic value in certain conditions.[3, 4] On the other hand, the blood may form a clot in the tissues and be subject to infection. The intraperitoneal injection of whole or citrated blood is used by many.[5-7] There is laboratory evidence that the blood cells thus administered soon pass into the circulation. The rate of absorption varies greatly, being very rapid under normal conditions and almost negligible in certain illnesses. Generally an ordinary intraperitoneal transfusion seems to require several days for 75 per cent of the blood to be absorbed. This method has given satisfactory results in a number of conditions, especially athrepsia, anemia, malnutrition, and prematurity. It is not suitable in cases of hemorrhage. It cannot be used in patients with diseases of the abdomen and its viscera or in moribund patients, as in these conditions the blood is not absorbed.[8] The main argument for its use is its ease of administration. It is not wholly without danger, as attested by case reports of intestinal perforation and hemorrhage from injury to the obliterated hypogastric artery.[9] Injection of the blood into the longitudinal sinus[2] through the anterior fontanel carries with it too much danger of perforating the meninges, with spread of blood over the cerebral cortex. The intravenous administration is a surgical procedure. It presents some difficulties, but these are readily overcome by adhering to certain technical details.

The technic here described has been consistently satisfactory. It overcomes in a direct manner the points of difficulty usually encountered. No claim is made as to originality,[1, 2, 10] as it is the assimilation of well-recognized basic principles in technic; however, a review of

the literature fails to find it accurately described. Likewise it is not maintained that this is the only satisfactory technic.

The internal saphenous vein as it courses anterior to the medial malleolus is generally used because of its constant position and the fact that it can be assumed to be patent in infants. The leg is properly cleansed and draped. Novocaine (½ per cent) is freely injected subcutaneously in the operative field. Digital pressure is then applied to

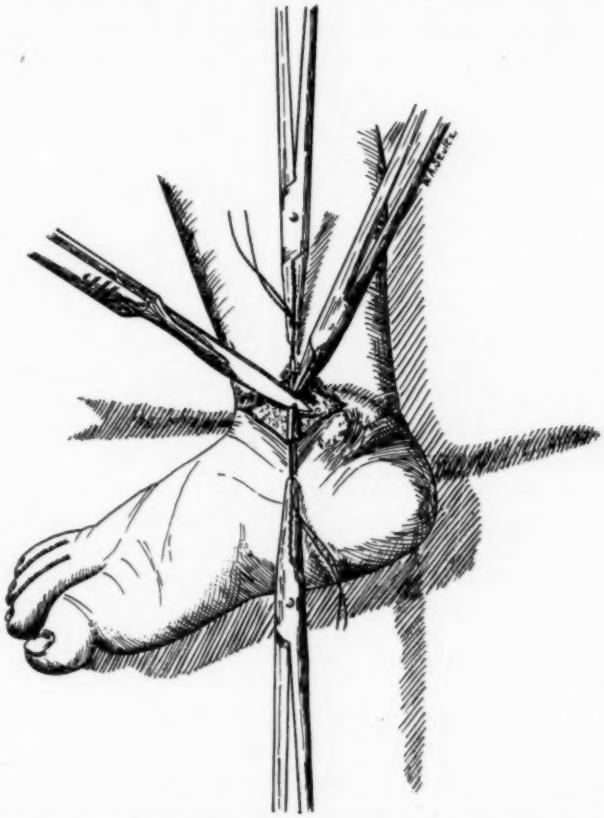

Fig. 1.—Vein immobilized by ligatures. Section of wall grasped with mosquito forceps. Opening made into lumen by incising portion of vein in bite of forceps.

disperse it so that it will not obscure the structures and landmarks. If the vein can be seen or palpated, it is well to let the point of needle puncture mark the site of the incision. A transverse incision about 1½ cm. in length is made through the skin anterior and just superior to the malleolus. The skin edges are separated by gentle blunt and sharp dissection. At this stage a tourniquet is applied a little above the incision. This distends the vein which lies under the superficial

fascia, and the blue color brings it into view. The tourniquet is not used throughout the procedure as the vein is delicate and when distended it is more easily injured. Once the vein is located, the tourniquet is released. The overlying fascia is carefully divided by blunt and sharp dissection. The empty vein is then freed on both sides and posteriorly for 1 cm. of its length by placing next to it the point of a closed pair of pointed mosquito forceps and opening the blades so as to separate the fibrous tissue alongside of it. Once the vein is freed, two strands of fine suture material are passed around it, one is tied

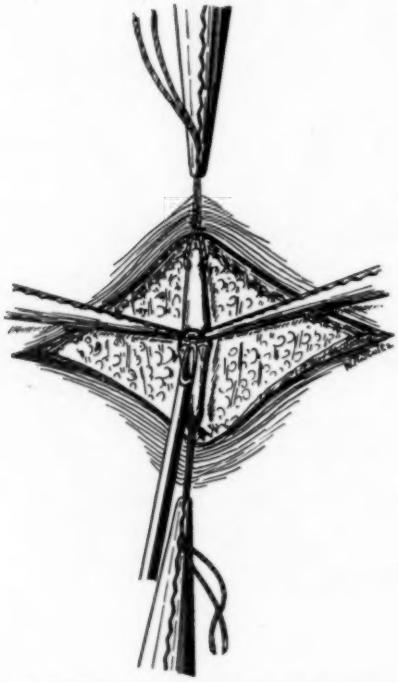

Fig. 2.—Vein held straight by ligatures. Mosquito forceps grasping edges of opening into lumen. Needle about to be introduced—passed through proximal ligature.

securely distally, the other proximally loosely with one loop. The ends, left long for traction, are grasped with forceps. The freed segment of vein is immobilized by slight traction on the ligatures. As it is seldom possible to insert a sufficiently large needle through the intact wall without its dissecting between the layers, it is necessary to make a clean-cut opening into the lumen. This is often a point of difficulty. A free incision with a scalpel is likely to fail to enter the lumen, also there is danger of its severing the vein. Sharp scissors[11] will generally accomplish the purpose; however, a safer method is to

grasp the vein wall for a portion of its circumference by a pointed pair of mosquito forceps. This fixes a section of the full thickness of the vein wall. An incision is then made into the lumen by passing a sharp scalpel along the distal surface of the forceps, being careful not to sever the vein completely. The forceps are removed. The edges of this incision are now separated so that the opening into the lumen is well established. This is accomplished by teasing them apart with the eye end of a medium-sized curved suture needle in a small needle holder. Once the edges are separated, the undivided portion of intima is recognized; with this as a guide, the end of the same needle is passed along it up into the vein. The edges of the opening are thus fully and safely separated. When introducing the transfusion needle or cannula, it is most important that the distal ligature be held sufficiently taut so as to hold the vein proximal to it straight, and that the proximal ligature be held just tight enough to prevent escape of blood. The proximal ligature is released as the needle approaches it. With the vein thus immobilized, if the opening into the lumen is gaping, a blunt 18 gauge needle may be inserted with ease and passed upward 2 to 3 cm. Otherwise the edges may be grasped with two pointed mosquito forceps and held apart. It is important that the needle be blunt, since a pointed needle would probably pierce the wall of the vein. The proximal ligature is now tied firmly over the needle so as to prevent the backflow of blood. The blood from the donor is introduced in any established method. While the blood is not being introduced, normal saline solution is slowly injected so as to prevent clotting. Upon completion, the needle is removed and the vein ligated securely proximal to the opening. The skin edges are approximated with fine sutures. If desired, the needle may be left in situ for the administration of an intravenous drip.

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# Critical Review

## PROBLEMS OF THE NEWBORN

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THE striking decrease in infant mortality since the turn of the century furnishes a splendid example of what can be accomplished by a group of interested individuals working in accord towards the same objective. The fruits of these efforts should serve as a stimulus for continuation of the good work until the so-called unpreventable minimum death rate estimated at 3 to 4 per cent and due chiefly to malformations is reached. In order to accomplish this it will be necessary to reduce the neonatal mortality which so far has failed to yield to anywhere near the extent that the mortality for the rest of the year has done. This outstanding failure has evoked the statements that mortality of the neonatal period has not changed materially in the last twenty or even fifty years.[1, 2, 3] While this is not exactly true, as will be shown later, the neonatal mortality rate has been so unyielding that there is little doubt that herein lies the greatest opportunity to salvage infant lives today.

### NEONATAL MORTALITY RATES

Table I shows what has been accomplished in the past twenty years in the reduction of the infant mortality rate during the first year of

TABLE I

MORTALITY RATES IN AGE GROUPS UNDER ONE YEAR AND PERCENTAGE DECREASE FROM 1915 TO 1935 IN THE U. S. REGISTRATION AREA*

| AGE GROUP | | 1915 | 1920 | 1925 | 1930 | 1934 | TOTAL PER CENT DECREASE |
|---|---|---|---|---|---|---|---|
| Under one day | Rate | 16.0† | 14.5† | 14.9 | 15.0 | 15.3 | |
| | Per cent change | | -9 | +3 | +0.1 | +2.0 | - 4 |
| Under one week | Rate | 31.8† | 28.9† | 28.1 | 27.1 | 26.4 | |
| | Per cent change | | -10 | -3 | -4 | -3 | -17 |
| Under one month | Rate | 46.5† | 41.2† | 37.8 | 35.6 | 34.0 | |
| | Per cent change | | -12 | -9 | -6 | -5 | -27 |
| Under one year | Rate | 99.9 | 85.8 | 71.6 | 64.6 | 60.1 | |
| | Per cent change | | -15 | -19 | -10 | -7 | -40 |

*Statistical information supplied by Mrs. Hope Bronzoni, Statistician, Vital Statistic Department, Utah State Board of Health.
†Estimated.

life, as compared with certain periods during the first month of life; the neonatal period. Thus, while there was a 40 per cent drop in the death rate under one year during this time, there was only a 27 per cent decrease in the death rate under one month and a 17 per cent reduction in the rate under one week. The smallest reduction, 4 per cent, occurred in the death rate under one day. However, when these figures were analyzed more closely it was found that actually the only decrease in deaths under one day occurred from 1915 to 1920. From 1920 to 1934 there was a gradual increase instead. About the same findings are noted in the statistics from England[4] and Germany[5] (Tables II and III). In Germany an unusual circumstance not found in England appears. This is an increase in the death rate for the first three days of life. In this country an increase is found only for the group under one day old and only from 1920. Findings of this nature—a rising mortality rate during the first day of life—show more forcibly than ever the importance of antenatal and natal factors in causing neonatal death.

This can be shown in other ways. Thus, deaths in infants less than a month old amounted to one-twentieth of the total number of deaths in all age groups in 1934. Deaths from all causes during the first month of life comprise about one-half of the deaths in the first year and about three-fourths of these occur in the first week. It is unquestion-

TABLE II

AGE DISTRIBUTION AND PERCENTAGE DECREASE OF INFANT MORTALITY (RATES PER 1,000 LIVE BIRTHS) FOR ENGLAND AND WALES

| AGE GROUP | 1906 TO 1910 | 1911 TO 1915 | 1916 TO 1920 | 1921 TO 1925 | 1926 TO 1930 | TOTAL PER CENT DECREASE |
|---|---|---|---|---|---|---|
| Under one day — Rate | 11.5 | 11.4 | 11.0 | 10.4 | 10.3 | |
| Under one day — Per cent change | | -1 | -4 | -6 | -1 | -12 |
| Under one week — Rate | 24.5 | 24.1 | 23.4 | 21.7 | 21.8 | |
| Under one week — Per cent change | | -2 | -3 | -8 | +1 | -12 |
| Under one month — Rate | 40.2 | 39.0 | 37.0 | 33.4 | 31.8 | |
| Under one month — Per cent change | - | -3 | -6 | -10 | -5 | -21 |
| Under one year — Rate | 117 | 109 | 91 | 75 | 68 | |
| Under one year — Per cent change | | -7 | -17 | -18 | -10 | -42 |

TABLE III

AGE DISTRIBUTION AND PERCENTAGE CHANGE IN INFANT MORTALITY FOR PRUSSIA (RATES PER 1,000 LIVE BIRTHS)

| AGE GROUP | 1901 | 1925 | PER CENT CHANGE |
|---|---|---|---|
| 0 to three days | 19.7 | 23.4 | +16 |
| 0 to ten days | 11.6 | 8.1 | -30 |
| Under one month | 59.4 | 43.4 | -27 |
| Under one year | 199.7 | 103.43 | -49 |

ably true, therefore, that antenatal and natal factors must be considered the most important causes of early infant mortality. In order to establish this fact more clearly to all there is need for the universal practice of subdividing neonatal deaths into the early (one week) and late ones (one week to one month).

REDUCTION OF NEONATAL MORTALITY ESSENTIALLY AN OBSTETRIC PROBLEM

The foregoing facts indicate clearly that the chief cause of failure to reduce neonatal deaths is an obstetric one. Its correction, likewise, is an obstetric problem dealing mainly with the prevention of deaths from prematurity and the effects of labor.

Whereas one would assume that generally improved public health measures in the past two decades would produce healthier babies born of healthier mothers and that there should be a resultant drop in the neonatal death rate, such has not been the case. In fact, as mentioned above, there has been an actual increase in deaths during the first day. Certainly this seems to be a paradox. Undoubtedly, however, some benefit must have been derived from improved health measures, and it probably has been obscured or counteracted by several factors which may be divided into two groups.

*Group I.*—Those due to contraselective factors largely beyond the control of obstetricians:

1. There has been a gradual relative increase in first-born children due to a general decrease in the birth rate, e.g., from 25.1 in 1915 to 17.1 in 1934. Owing to the greater hazard in first born naturally a corresponding increase in neonatal mortality would be expected.

2. The age of women bearing children for the first time has increased. This also constitutes a greater birth hazard to the child because it is generally recognized that labors in elderly primiparas are more likely to be prolonged and prematurity is more common than in younger individuals. Nathanson[7] and Roeder[8] have recently shown this to be true. They found in women over thirty-five years old a greater number of complications of pregnancy and labor and an increased incidence of operative deliveries. As would be expected the fetal mortality was considerably higher.

3. Improved health measures bring to labor a greater number of women physically unfit to withstand the rigors of pregnancy and labor or to propagate vigorous offspring. In other words there probably are more weaklings born.

Such contraselective factors, no doubt, play some part in producing early neonatal deaths, but even so it must not be blandly assumed that they are solely responsible for the unyielding death rate. Other factors which incriminate some of the increasingly popular obstetric practices must be responsible too.

*Group II.*—Those due to factors possible of control by obstetricians:

1. The promiscuous and injudicious use of anesthetics and analgesics probably plays a subtle rôle in maintaining the high neonatal mortality rate. Regardless of the glowing reports of numerous enthusiasts there are gradually creeping into the literature reports of the ill effects of the preparations in use not only upon the child directly but also indirectly through prolongation of labor.[9-14]

For obvious reasons not all the deaths due to these causes are reported as such. Furthermore, it is not always possible to determine which of the late neonatal deaths are primarily caused by anesthetic effects.

2. The acknowledged increasing operative trend which has been deplored by so many authorities who continue to uphold and teach sane conservative obstetric practices.[15-19] They condemn and implicate unnecessary or unindicated use of methods of induction, forceps, versions, and cesarean sections as very responsible factors in the causation of fetal deaths. In this group should be included operative deliveries due to the unrecognized retarding effect upon labor of analgesics and anesthetics.

3. The indiscriminate administration of posterior pituitary extract before birth regardless of the dilatation of the cervix uteri or the presence of disproportion between the fetus and birth canal. This probably has a definite but unascertained influence upon neonatal mortality.

The factors mentioned in Group II are largely controllable and to some extent at least one factor in Group I is controllable. This is prematurity. It has been estimated[20, 21] that from 30 to 50 per cent of neonatal deaths including prematures and stillbirths are avoidable. This makes it questionable whether or not obstetricians should indulge in the common practice of regarding deaths from prematurity as unavoidable. Ehrenfest[22] states, "It seems fair to assert that the obstetrician cannot any longer, for statistical or any other purposes, coolly deny all responsibility for the death of a newborn infant below 2,500 grams." This responsibility consists not only of the use of the least dangerous methods of delivery for prematures[23] but also of antenatal care aimed at prevention of prematurity. If the incidence of prematurity is to be reduced it must be done by the physicians caring for women during pregnancy. Certainly there seem to be sufficient data at hand to reiterate that the chief cause of failure to reduce neonatal deaths is an obstetrical one. Until there is more interest displayed by obstetricians little can be accomplished along these lines.

Persistence for years of a higher neonatal mortality rate in urban rather than rural districts is contrary to what one would expect. This situation only serves to illustrate the effect of some of the factors mentioned in Group II. It also indicates irrefutably, regardless of attempts to explain otherwise, that meddlesome obstetrics is the vogue[24] in cities. These criticisms are not new but obstetricians have continued to ignore them. There is no further ground for excuse and their complacency in the face of this criticism is to be condemned. Especially is this true of those who continue to exploit as safe for the country as a whole, operative and anesthetic procedures requiring assistance and equipment incapable of being duplicated in many places. Furthermore, the editors of medical journals which publish such enthusiastic reports must come in for some criticism in accepting for publication reports based on inadequate methods or unreliable data. So far the feeble efforts of the few conscientious ones to reduce neonatal mortality have been nearly submerged by the deluge of articles on operative procedures and methods of anesthesia which cannot help but increase the toll of lives. Montgomery[13] has only recently been led to say, "Apparently something is wrong with methods of management of labor, and saddest to relate, whatever is wrong is going more astray with each succeeding year.

Probably a number of matters are at fault, but of this complex problem I believe that obstetric amnesia, analgesia, and anesthesia constitute an important portion."

Fortunately, there are a few examples of what may be done to improve existing conditions. They are found in the data published by some of the large maternity institutions,[25, 26] which show that extended efforts in every direction will definitely reduce neonatal mortality. It has been brought about chiefly through reducing the incidence of prematurity. The recent report of Clifford and Irving[27] inferentially reiterates this point. It is of much more importance in illustrating the salutary effects of a concerted attempt to reduce neonatal mortality than in proving the harmlessness of certain analgesics used in labor during a period when, as previously reported by Clifford,[25] there has been a rapidly declining death rate due to a decrease in the incidence of prematurity. So far the effect of analgesics upon neonatal mortality has not been determined satisfactorily one way or another. This is due to the difficulty of finding a method of approach sufficiently free from complicating factors to permit accurate deductions not subject to criticism.

## CAUSES OF NEONATAL DEATH

It is nearly impossible to obtain reliable statistical information regarding neonatal mortality by consulting the Census Bureau Reports. There are two important reasons for this, neither of which is the fault of the Bureau: (1) the method of tabulating certificates and (2) the method of certifying deaths.

### I. METHOD OF TABULATING

The International List of Causes of Death[28] used by the Census Bureau is so inadequate that many diseases are obscured by the general title under which they are filed or the titles are so vague that a given disease may be filed under several headings. The list which is given below illustrates these difficulties:

XIV. Congenital Malformations.
- 157. Congenital Malformations (stillbirths not included).
  - (a) Congenital hydrocephalus.
  - (b) Spina bifida and meningocele.
  - (c) Congenital malformations of the heart.
  - (d) Other congenital malformations.

XV. Diseases of Early Infancy.
- 158. Congenital debility.
- 159. Premature births.
- 160. Injury at birth
  - (a) Cesarean section.
  - (b) Without cesarean section.
- 161. Other diseases peculiar to early infancy.
  - (a) Atelectasis.
  - (b) Icterus of the newborn.
  - (c) Sclerema.
  - (d) Others under this title.

Perusal of the list of terms included under the various titles given above brings out more glaringly some of the faults that need correction. A few examples will show how the incidence of a certain cause of death

may be obscured by the manner in which deaths are filed. The vital statistic clerk cannot always be blamed for this because of failure to query the physician about an ambiguous assignment of death. The difficulty may be due to ambiguity of the list itself. For instance some of the following are included under the subtitles of the list:

158. Congenital Debility.
Congenital dyspnea.
Atresia of the lung.
Heart failure.
Congenital respiratory paralysis.
Failure of cirulation.
Paralysis of the lung.

160. Injury at Birth.
Apoplexy neonatorum.
Birth embolism.
Inspiration of mucus.
Suffocation in childbirth.

161. (a) Atelectasis.
Imperfect inflation of lungs.
Collapse of the lungs.

161. (b) Others Under This Title.
Undeveloped lung.
Asphyxia neonatorum.
Congenital cyanosis.
Cyanosis.

Surely such a method of tabulating cannot be very informative to one searching for the incidence of a given disease for the actual cause of death indicated by nearly any of these terms might be atelectasis, pneumonia, congenital heart disease, or possibly intracranial trauma. This is only one of the many difficulties that may be encountered in the present list.

Especially pernicious is the classification congenital debility, which is used more or less as a dumping ground for deaths difficult to assign. This title together with three others used by the census bureau in special reports, e.g., Unknown or Ill-defined, All Other Causes, and External Causes accounted for one-twelfth of the total death rate under one month of life in 1934. It is, therefore, obvious, that there is a not inconsiderable group of neonatal deaths about which nothing can be ascertained.

## II. METHOD OF CERTIFYING

Carelessness, indifference, or ignorance upon the part of physicians adds to the difficulty of properly tabulating deaths, causing, thereby, indefinite delay by necessitating the sending of queries to physicians. Primarily these difficulties are due to inadequate medical training, a factor which is being gradually corrected although even at present the curriculums of most medical schools are deficient in respect to the newborn. Because most medical men in practice today have received better training it would seem unnecessary now to permit the use of so many vague terms in the certification of deaths.

In summary it may be said that owing to overlapping and ambiguity of terms found in the International List of Causes of Death, as well as to carelessness, indifference, and ignorance upon the part of the medical profession in certifying deaths, the reports of the Census Bureau are grossly inaccurate and, therefore, largely valueless for use in making studies of a detailed nature.

Correction of this situation will be difficult. One approach is the adoption of a new classification of causes of death, either through revision of the International List or by creation of a more satisfactory

classification by the Census Bureau itself. Owing to the fact that the list used is an international one it may not be possible to include all the changes desired. In case of refusal of the Census Bureau to deviate from the International List there is another approach. This is the creation by pediatrists and obstetricians in the United States of a suitable standard classification of the causes of death for use by hospital librarians. Data would then be available for more extensive studies of the causes of neonatal death. Again, the research division of the Children's Bureau might conduct a study of neonatal mortality similar to the most valuable one recently made in respect to stillbirths.[29] Finally it will be necessary for medical schools to include in their curricula a greater amount of time devoted to the study of the newborn. After all this is the only way in which doctors can be made to realize what a fertile field the newborn infant offers for reduction of infant mortality. Unfortunately, our knowledge of the newborn infant is too scanty. Such a state of affairs indicates the need for a comprehensive study of this age group. The fact that there exists nowhere in the United States or in the world, for that matter, an institution primarily devoted to neonatal research illustrates the decided lack of interest in this branch of medicine up to the present time. The need for such an institution is beyond dispute. Therefore, one should be established.

### ACCURATE CERTIFICATION OF DEATH

Greater accuracy in certifying deaths is indispensable if the neonatal mortality rate is to be reduced. Authentic information in regard to deaths due to preventable causes will make it possible to place the blame where it properly belongs. As a result of this efforts to prevent these deaths will be more successful. Furthermore, accurate certification means improved diagnostic technique which in turn means that lives will be saved through early recognition and treatment of neonatal disease.

Accuracy of certification by doctors is dependent upon several conditions. There is need for a greater number of postmortems upon newborn babies and these autopsies should be done more thoroughly. Since neonatal pathology differs considerably from that of older children physicians should become better acquainted with these differences in order that the cause of death may be ascertained more satisfactorily. The ability to know where and what to look for will often make it possible to detect a causative factor which otherwise escapes notice. When autopsies cannot be obtained there still are means that may be used to determine the cause of death. These consist of laboratory procedures which can be carried out after death. Finally, close watch for certain signs and symptoms that frequently escape notice before death may be sufficient to make clear a diagnosis which, otherwise, might be missed.

### COMMON CAUSES OF DEATH

The simple pathologic classification (Table IV) that Cruickshank[30] used in his study of 800 neonatal autopsies serves admirably as an aid to the pathologist in indicating what to look for. A subgroup may be added to include the inconsiderable number of deaths from the hemorrhagic diathesis. Cruickshank places them in the infective group and other hemorrhages rightly under birth effects. Studies of this nature

TABLE IV

CRUICKSHANK'S CLASSIFICATION OF CAUSES OF NEONATAL DEATH

| | NO. | PER CENT |
|---|---|---|
| 1. Birth effects (asphyxia, atelectasis, injuries, prematurity) | 540 | 67 |
| 2. Infective conditions | 238 | 30 |
| 3. Gross congenital malformations | 22 | 3 |

give information of accuracy unequalled in ordinary vital statistics reports in which the causes of death are based to a large extent upon clinical diagnoses that are often a matter of conjecture. When the classification shown in Table IV is considered in more detail it is of value in illustrating the common causes of death. If an autopsy is performed upon a newborn infant dying before a diagnosis is made knowledge of the relative frequency of these causes may help indicate where to look and what to look for.

*Birth Effects.*—Deaths in this group might be called delayed stillbirths for the pathology found in these infants at autopsy for the most part is similar to that found in stillborn infants, namely, asphyxial hyperemia, hemorrhage, and atelectasis. These deaths are due to antenatal and natal rather than postnatal causes and for this reason a goodly portion of them may be considered preventable. Most neonatal deaths are included in this group. Cruickshank so tabulated 68 per cent of his cases. Death usually occurred in the first few days of life and nine-tenths of them in the first week. Practically all showed signs of asphyxia. While it would be better to separate these deaths into those due to asphyxia alone or those associated with birth injury for practical purposes this is difficult. Hemorrhage of variable degree may be the result of either asphyxia or birth injury but it is not always possible to determine which. Some earlier observers found a rather high incidence of intracranial hemorrhage considered for the most part due to birth trauma. Thus, Warwick,[32] Rodda,[33] and Ehrenfest[34] noted it in about 50 per cent of all infants dying in the first weeks of life. In recent reports the incidence has not been so high.[31] Cruickshank found it the cause of death in only 20 per cent of his necropsies and Von Haam,[35] in 16 per cent. This has been the experience of others so it appears that there is a decreasing incidence of death due to intracranial hemorrhage. It may be, however, that while hemorrhages are just as frequent not as many are considered sufficient to cause death. Under such circumstances it is probable that such deaths are attributed to asphyxial conditions and that the hemorrhages are considered to play a secondary rôle. It might be mentioned here that although autopsy records show fewer deaths due to intracranial hemorrhage vital statistic reports show an increase in the death rate from this cause. The explanation for this is that owing to the great medical interest in the subject in the past fifteen years there has been an increasing trend by doctors to certifying that deaths are due to this cause.[36]

*Infective Conditions.*—Death from infections occurred in 30 per cent of Cruickshank's cases. The half that showed multiple foci of infection were classed as cases of septicemia although a large number of these showed evidence of pneumonia. In fact pneumonia was so common that it was observed in 83 per cent of the infants dying from infection. These findings are similar to the reports of others. Browne[37] demonstrated pneumonia in 26 per cent of his necropsies and thirty-one per

cent of the deaths in the first week of life were due to this disease. Johnson and Meyer[38] report that in 19 per cent of their 500 autopsies on newborn and stillborn infants pneumonia was present. Helwig[39] found that 41.5 per cent of his cases revealed pneumonia sufficiently extensive to constitute an important factor in the death of the baby. Hess-Thaysen's observations[40] made years ago are of interest. In his first series of neonatal autopsies he found only 8 per cent with pneumonia but when he began to pay particular attention to the subject he was able to demonstrate it in 42 per cent. All of these studies point to the important part pneumonia plays in neonatal mortality.

A large number of infective deaths, including pneumonia, are due to the indirect effects of birth. Especially is this true of factors which predispose to maintenance of the atelectatic state or to asphyxial conditions in general. Among these may be included birth trauma, prematurity, and narcosis. The partially expanded and hyperemic lung seems especially liable to pneumonia. To a large extent deaths from infections are preventable.

Cruickshank found a low incidence of syphilis, 0.75 per cent. This agrees with the findings of other investigators.[25, 31, 41] Observations of this sort emphasize that it is impossible today to attribute many neonatal deaths to this disease, as was done so commonly years ago. The same may be said for fetal endocarditis. Cruickshank found no case in which there was evidence of endocarditis even if sepsis neonatorum was present. In Dunham's report[42] of 39 cases of septicemia no evidence of endocarditis was noted in the infants coming to autopsy. This peculiar immunity of the heart to sepsis substantiates the view that endocarditis is rare at birth.

*Gross Congenital Malformations.*—Malformations accounted for only 3 per cent of Cruickshank's series. This confirms the relative unimportance of such conditions as a cause of death. Seventy-five per cent of these involved the central nervous system. In only three of the 22 malformations could death be attributed to congenital heart disease. His findings add emphasis to the view now held by many, that cardiac abnormalities are rarely the cause of neonatal death. Most of the deaths ascribed to this cause are actually due to asphyxia.

## SUDDEN DEATH

Death without warning probably occurs most often during the neonatal period than at any other time of life. The reason for this is that at no period of life is there so much opportunity for disorganization of vital functions. Sudden or unexpected deaths are invariably accompanied by an element of surprise and often they may seem most difficult to explain. Actually, however, the explanation may be relatively simple. The lesions which produce sudden death at this age are much more limited in number than in older individuals who have had time to acquire many of the acute and chronic diseases the sequelae of which play a subtle rôle in the production of these deaths. While the cause of death may be presumed with a fair degree of accuracy by the external appearance of the body, the circumstances attending death and other factors having to do with the type of labor and the mode of delivery, the actual cause is revealed only by a thorough autopsy.

Sudden death during the neonatal period usually terminates in one of three types of agonal seizure or a combination of them—cyanosis, convulsion, or pallor. Most of these deaths occur within the first day or two of life and are caused by a massive lesion save in prematures where immaturity of the respiratory tract alone may be the chief factor. In mature infants sudden disorganization of the vital functions is most often caused by intracranial hemorrhage due to birth trauma.[34, 43-45] When sudden death occurs at the height of an unheralded cyanotic attack the hemorrhage is nearly always located beneath the tentorium where it causes paralysis of the respiratory centers in the medulla. The amount of blood may not be large. The type of lesion is responsible for most of the sudden deaths in the first hours of life. In this type of hemorrhage convulsions are infrequent for death often occurs before the intracranial pressure is sufficiently high to cause cortical irritation. However, if death is delayed a convulsion may occur. Sudden death from supratentorial lesions usually appears at a somewhat later period for impairment of the centers in the medulla does not come on as early. Therefore, pallor rather than cyanosis is the rule at first and the agonal attack is usually ushered in with a convulsion. Ventricular hemorrhage is rarely a cause of unexpected death, but when it does occur severe cyanosis and a tonic convulsion with trismus is usually observed. Mature infants are rarely affected. Lesions of the spinal cord are responsible for sudden death more often than is ordinarily supposed, especially after breech deliveries.[46, 47] For that reason no autopsy should be considered complete without exploration of this structure. Death occurs immediately if the lesion is high enough to involve the phrenic nuclei. Apnea, pallor, and flaccidity of the extremities are the only associated symptoms.

Among the less frequent causes of early sudden deaths are hemorrhages and ruptures of intrabdominal viscera due to birth trauma. The liver and spleen are the organs usually involved although rupture of the intestine with extensive hemorrhage has been reported. Usually the infant dies in the first few hours of life but occasionally it lives for a few days and dies suddenly.[48] Pallor from hemorrhage and shock is the only symptom. Suprarenal hemorrhage is more often the cause of sudden death from unknown origin than ordinarily supposed. Ehrenfest[49] states that hemorrhages may be found in the adrenals in five per cent of infants coming to autopsy. This has not been our experience. Death follows sudden pallor and shock from hemorrhage or adrenal insufficiency of the adrenal and consequent hypoglycemia.[50] The occurrence of cyanosis and convulsions in some cases tends to confuse the picture.

When sudden death occurs at a later period, that is after the infections have had a chance to develop, unrecognized sepsis or pneumonia is the most frequent cause. Death follows severe cyanotic attack with or without convulsion. Although congenital heart disease is commonly certified as the cause of sudden death this is most unlikely. The same may be said for thymic deaths in the newborn.[51, 52] If death occurs from this so-called syndrome it is rare in the neonatal period.

### AIDS IN DETERMINING CAUSE OF DEATH

When it is impossible to obtain autopsy permission consideration of a few of the factors associated with the death may help one to give a

presumptive opinion of the cause of death with a fair degree of accuracy. Such factors are of value also in indicating the most likely place to look for pathology when an autopsy is made.

*Age at Death.*—The age at which the infant dies is of assistance in pointing to the cause of death. Neonatal deaths may be divided into those occurring early and late. Early deaths are limited to the first week of life. If they occur in the first three days they are practically always due to the direct effect of labor. In the occasional deaths due to malformations the cause is perfectly obvious. The nearer death occurs to delivery the greater the likelihood of death from birth effects, of which asphyxial conditions and intracranial injuries are the most common. One should, therefore, expect to find lesions in the lungs or within the cranial cavity. If death occurs from three days to one week the same causes are to be thought of first but deaths from infections begin to appear. Since pneumonia constitutes the greatest cause of infective deaths the lungs will be the seat of the pathology in the majority of instances. Late deaths, occurring from one week to one month, are often the result of acquired disease and the later the death the more likely is this to be true. The causes of death in this group consist chiefly of infections, such as pneumonia and localized infections, or less commonly of diseases of the blood—hemorrhagic disease, hemolytic jaundice, erythroblastosis. Delayed deaths from the more obscure types of congenital malformations occur in this period but the incidence remains low.

*Maturity of Death.*—The gestation age and size of the baby help to indicate the probable cause of death. Prematures most often die early from the effects of immaturity which are associated with asphyxial signs and a variable amount of atelectasis. These conditions may be brought about or be aggravated by the use of anesthetics and analgesics during labor. Thus, Dunham and McAlenny[53] found a higher death rate in premature infants whose mothers had received morphine before delivery than in those who had received none. Birth trauma and infections are the next most common causes of death in prematurely born infants. It is generally recognized that prematurity favors the incidence of intracranial hemorrhage[54] as well as the incidence of postnatal infections. Dunham and McAlenny found the former accountable for one-sixth and infection for one-fourth of the deaths in premature babies. Late deaths in this group are usually due to the infections or inanition.

Excessively large babies die most often from birth injuries or the hemorrhages resulting from them. A ruptured viscus must not be overlooked in these babies. In obscure cases it is possible that death is due to overactivity of pancreatic function and resulting hyperinsulinemia, the consequence of a maternal diabetes.[55, 56] Toxemias of pregnancy may be responsible for death from renal or intracranial thrombosis in robust mature babies according to Cruickshank.

*The Mode of Delivery.*—This has some bearing on the type of death. Breech deliveries,[57] including internal versions and extractions, prolonged labor, and forceps deliveries are noted for their traumatizing effects upon the baby. Most common are the intracranial injuries, usually tentorial lacerations. The cause is usually a combination of trauma, anesthesia, and shock with resulting paralysis of the respiratory center.

In combination with the traumatic shock anesthesia may assist in paralyzing the respiratory center. One must not overlook the fact that traumatic deaths of this sort may follow normal or precipitate labors. Pituitary extract administered before delivery is an etiologic factor here. In respect to anesthesia and analgesia it is likely that this plays a more important part than one would assume by aggravating the depressing effect of operative deliveries upon the respiratory centers. If death does not ensue immediately there may be an indirect death later on caused by the prolongation of the partial atelectatic state which favors the development of pulmonary infections. In such cases the lungs would reveal the presence of asphyxial pathology and pneumonia.

*Antemortem Observations.*—With the exception of cases of sudden death the record of certain signs and symptoms observed closely during life may be of distinct value to the physician or pathologist in indicating the probable cause of death, regardless of whether or not an autopsy is performed.

Cyanosis is the most common symptom of neonatal disease. According to my estimations roughly 85 per cent of all infants dying at this period of life manifest cyanosis to some degree. In spite of this the symptom may be utilized by virtue either of its absence or its presence, in which instance the character or association with other symptoms is important. Absence of cyanosis is suggestive of the fact that neither the respiratory tract nor the respiratory center is interfered with primarily. By excluding the air passages and cranial cavity the cause must be sought in the infections, blood diseases, congenital malformations, and metabolic disturbances. When cyanosis is present it may be divided into the persistent and intermittent types. Persistent cyanosis is usually due to pulmonary infections, the marked atelectasis of prematurity, congenital heart disease, and fixed obstruction to the upper air passages. Intermittent cyanosis is more likely the result of increased intracranial pressure, moderate atelectasis associated with other disease, or transient obstruction to the air passages such as mucus. When cyanosis is associated with other symptoms the diagnosis is further narrowed down. In conjunction with convulsive twitchings or convulsions intracranial pathology should be looked for. Its association with obstructive breathing indicates occlusion of the upper air passages by mucus, infections, or anomalies which include intrinsic or extrinsic tumors. When severe jaundice and cyanosis occur together sepsis is the first consideration. Uncomplicated cyanosis in mature infants indicates primary pulmonary pathology. Hunt's analysis[58] of 118 postmortem examinations in respect to the frequency of the pathologic lesions causing cyanosis in the newborn infant summarizes the situation splendidly. Intracranial lesions including both meningeal hemorrhage and severe tentorial tears were the most frequent lesions. The symptoms appeared early. The most common single lesion was pneumonia. Presence of a hyaline membrane due to aspirated amniotic sac contents was relatively common, and was associated with persistent cyanosis. Cyanosis due to congenital heart disease was uncommon and other causes such as septicemia, diaphragmatic hernia, and meningitis relatively rare. Dunham[59] quite rightly points out that death from atelectasis must always be considered secondary to some condition interfering with the respiratory mechanism which brings about full expansion of the lungs. In all probability atelectasis should never be certified as the primary cause of death.

Convulsions are frequent during the neonatal period. Inasmuch as the nervous system at this age probably does not respond convulsively to anything but gross insults these attacks usually are predicated on demonstrable lesions within the craniovertebral canal. The causes of convulsions may be classified as follows:

| Organic Convulsions | Functional Convulsions |
|---|---|
| Traumatic | Agonal |
| Infective | Toxic |
| Congenital Malformations | Metabolic |

Organic convulsions are by far the most common and are due to traumatic intracranial hemorrhage or edema in the majority of instances. Hemorrhagic disease need hardly be considered. The lesions of intracranial hemorrhage have been considered briefly in the discussion of sudden death. Associated symptoms are cyanosis, bulging fontanel, and thermic instability.[60, 61] In the infective group the meningitides occupy first place although meningo-encephalitis of septic or syphilitic origin must be mentioned. Cruickshank found meningitis in 4 per cent of his autopsies. A great variety of causative organisms have been reported but the pyogenic bacteria are the usual offenders. However, one must not overlook the possibility of meningococcic infection because recovery may be brought about by serologic treatment.[62] In the majority of instances meningitis is acquired and for that reason death occurs in the late neonatal period, i.e., after the first week. The possibility of intrauterine infection does not come into the picture here to any extent for this type of infection usually causes intrauterine death. If the infection is less virulent the infant survives. In such instances retardation of cerebral development may cause confusion of this condition with cerebral birth injury.[63] Convulsions due to infections elsewhere in the body are considered in the functional group. Congenital malformations are responsible for convulsions and death in a small number of cases. It is possible, however, that convulsions in nonfatal cases may be the result of developmental defects more frequently than one would think.[64] These consist of aplasia, hypoplasia, and atrophic lobar sclerosis. The malformations which are responsible for convulsions and death in the neonatal period are relatively simple to detect. They include anencephaly, hydrocephalus, encephalocele, porencephaly, oxycephaly, and microcephaly.

Functional convulsions comprise a small group about which little is known but considerable speculation exists. Recognizable pathology is not found in the brains of these infants. The agonal form is less common in newborn infants than in older infants because the neonatal central nervous system is not particularly responsive to other than major insults. When such convulsions occur they are usually the result of an agonal asphyxia or anoxemia. They are often associated with some of the infections.[65] In some instances they might be placed in the toxic group. Included under this heading are convulsions due to bacterial or maternal toxins. Tetanus neonatorum represents the most common of the bacterial group. It is considered relatively uncommon in civilized countries but Hines[66] points out that it is a much more frequent cause of death in the United States than is ordinarily supposed. The umbilical wound is the atrium. Maternal toxins have been considered a rather

frequent cause of convulsions but it is doubtful if this is true. Occasionally the infant of an eclamptic mother dies a few hours after birth in convulsions. While in rare instances maternal toxins may be responsible usually there is some recognizable intracranial pathology. Most of these infants are premature or immature and the convulsions are due to intracranial hemorrhage during the eclamptic seizure of the mother or while the child is being delivered by some manipulative procedure. When this is not the case intracranial thrombosis, which in some manner seems linked with maternal toxemia, may be found. The metabolic convulsions are found in some of the rarer forms of neonatal disease. They may appear in infants of diabetic mothers and are more likely to be due to physiologic hyperactivity of the islands of Langerhans than to hypertrophy or hyperplasia of these cells.[67, 68] In other cases the hypoglycemic tendency of the first days may be aggravated by adrenal and intracranial hemorrhage. It has been reported consistently in the former.

So-called tetany of the newborn belongs in this group of convulsions. From the standpoint of being a frequent cause of death the subject needs little consideration here. However, owing to the fact that there has been some controversy about its existence in the past few years it will be mentioned briefly. Earlier texts (Von Reuss,[69] Grulee[70]) questioned whether characteristic symptoms of tetany had been observed in the newborn infant. More recently Shannon,[71] Nesbit,[72] Bass and Karelitz[73] and others have attributed as manifestations of tetany a number of symptoms formerly considered indicative of cerebral irritation from birth trauma (hyperirritability, hypertonia, hyperpyrexia, muscle spasms, vomiting, cyanosis, convulsions). So far most of the evidence upon which this concept has been based is more speculative than factual. Few autopsies have been performed because the infants have recovered. Blood chemistry studies have been infrequent and fractional blood calcium analyses[74] or estimations of the inorganic phosphorus concentration have been rare, indeed.[75] Blood calcium determinations have not always conformed with the picture typical of tetany, that is, a serum calcium content below 8 mg. per 100 cubic cm. In fact the phosphorus radicle has received too little attention. Specific symptoms usually considered pathognomonic of the disturbance (Erb, Trousseau, Chvostek) have not been obtained in all cases for several reasons. Thus, the Erb test for electrical irritability has been omitted, as a rule, because infants at this period normally have increased electrical irritability. The Trousseau phenomenon has been impossible to elicit frequently because of rigidity of the infant. Finally, the Chvostek facialis sign, upon which many of the diagnoses have been based, is considered by many as a normal response in the newborn infant.[68, 76] From the foregoing it is obvious that the entire subject requires more intensive study and we are indebted to the investigators who have opened up this subject again. At present the evidence is insufficient to warrant the contention that tetany in the newborn infant is relatively common. In spite of careful observation we have been able but rarely to suspect the possibility of tetany in newborn infants under our care. In regard to prompt response to calcium therapy Tow states that he has often seen the symptoms of nervous irritability which these observers would have us believe are due to tetany disappear in a few days by "intelligent neglect." Probably some of the controversy

has been caused by a failure to differentiate clearly between the well known rachitic and lesser known nonrachitic forms of tetany,[77] as well as a failure to identify the etiologic factor involved. Assuming that the nonrachitic form of tetany is present alkalosis and hypoparathyroidism are probably the most important underlying conditions. In this form of tetany hypocalcemia is not always present in which case the diagnosis must be based on electrical reactions. So far this has not been done. The factors which might be responsible for these conditions are primarily obstetric ones and preventable to a considerable extent. Deficient fetal calcium is an antenatal factor due to an insufficient maternal supply or the inability to utilize an adequate supply. Here maternal vitamin D deficiency or maternal toxemias may possibly be found to play a distinctive part. This might explain Flood's[78] finding of lowered calcium values in infants born by cesarean section. Alkalosis with tetanoid symptoms may be due indirectly to the natal factors responsible for cyanosis, anoxemia, shallow breathing, and vomiting. Among the common ones are atelectasis, intracranial trauma, or anesthesia and analgesia. Hyperventilation, the result of resuscitative measures, might cause alkalosis by consequent washing out of the carbon dioxide in the lungs. However, up to the present tetany from hyperventilation and vomiting have not been demonstrated. Hypoparathyroidism may be a natal factor appearing as a result of hemorrhages into these structures or hyperactivity of the glands during pregnancy. Lesions of this nature were mentioned frequently in the autopsy records of older writers, but of late little attention has been paid them. To sum up one must maintain an open mind about the existence of tetany of the newborn. Those who have drawn attention to the subject should be complimented for stimulating research in a scantily studied field. However, we cannot agree with Shannon that proof of the common existence of tetany of the newborn will relieve the "oppression" of the obstetrician. It will continue to remain an obstetric responsibility because it must be considered preventable to a large degree.

Jaundice of sufficient intensity to be an outstanding symptom in infants dying in the neonatal period is not especially common. When it is present it may be of value in pointing to the cause of death. Astrachan[79] found that of all the pediatric patients with jaundice coming under his observation 45 per cent were newborn babies and over 60 per cent of these died. Only the rapidly progressive and fatal forms of jaundice need be considered here for it is obvious that the innocuous so-called physiologic icterus neonatorum or the exaggerated icterus of prematurity may be excluded. Deaths in which the symptoms of jaundice predominate may occur early or late. In the former, jaundice is present at birth or appears in the first twenty-four to thirty-six hours rapidly increasing in intensity. This form is often familial and is associated usually with an enlarged spleen and liver. It constitutes the form of jaundice designated by the term icterus gravis neonatorum. Yellow stained amniotic fluid, golden yellow vernix caseosa, and an oversized placenta are suggestive that this type of jaundice may develop in the offspring. The association of a varying degree of jaundice, hemolytic anemia, erythroblastic activity in the peripheral blood, and edema, in many of these patients has led to the recent use of the term erythroblastosis fetalis as a generic heading for all of these more-or-less

interrelated conditions.[80-82] Hawksley and Lightwood[83] have portrayed the possible relationship in the following manner:

Erythroblastosis Fetalis

| Intrauterine (usually stillborn) | Neonatal |
|---|---|
| 1. With universal edema = hydrops fetalis | 1. With severe jaundice and anemia = icterus gravis neonatorum |
| 2. Without edema | 2. With severe anemia and little or no jaundice = anemia hemolytica neonatorum |

When symptoms of cerebral irritation (muscle spasms, general convulsions) are associated with jaundice nuclear icterus or kernicterus may be suspected.[84, 85] At autopsy intense icteric pigmentation of the nuclear masses of the brain is found with or without degenerative changes. Erythroblastosis may be present. In most of the early deaths in which jaundice has been a prominant symptom the onset is shortly after birth, progress is rapid, and termination occurs in three or four days. Occasionally, however, jaundice does not appear until the third or fourth day. In this instance, especially when there is associated cyanosis, sepsis must be considered. This condition is responsible for most of the late deaths, which comprise perhaps, the largest number of late neonatal fatalities. Astrachan found jaundice present in 45 per cent of his cases of sepsis neonatorum. Dunham reports that icterus was peculiarly but consistently absent in the streptococcus septicemias and present in over one-half of the staphylococcus and colon bacillus infections. It is very probable that sepsis may be responsible for a large number of deaths rather generally attributed to icterus gravis neonatorum. The same may be said for Winckel's and Buhl's disease. However, full substantiation of this opinion must rest upon the more routine use of blood cultures in obscure cases of jaundice. Presence of vomiting, diarrhea, cyanosis, and possibly fever is suggestive of some form of sepsis. Knowledge of this should lead to a search for the portal of entry. The common atria are skin lesions, umbilical infections, and pulmonary or alimentary tract infections. In a very small number of cases jaundice is due to syphilitic hepatitis. Congenital obliteration of the bile duct does not hold a conspicuous position as a cause of death as formerly believed. It is characterized by obstructive jaundice from birth, acholic stools, and liver enlargement. In the rare case of atresia of the duodenum below the ampulla of Vater jaundice is associated with the usual symptoms of intestinal obstruction and vomiting of bile. In summary, early deaths following early appearance of progressive icterus, as a rule, indicate disturbance of the hematopoietic system which may be demonstrated at autopsy. Late deaths following tardy jaundice usually may be attributed to sepsis which can be proved by blood culture as well as autopsy. Deaths from these causes, however, do not comprise a very large group of cases.

Pallor in infants dying suddenly and at an early period has been referred to under the caption sudden death. In these infants pallor appears suddenly and is due most often to internal or external hemorrhage. A few deaths occur at this period the causes of which are related in some way to defective hematopoiesis and sometimes associated with

a varying degree of edema or jaundice.[86-88] These conditions have been tacitly grouped under the general heading erythroblastosis fetalis. Not all of these children die early, however, and one form usually called primary anemia of the newborn is rarely fatal. The pallor occurring in the secondary anemia of sepsis must be mentioned although it is usually masked by cyanosis or jaundice.

Temperature curves of infants dying in the neonatal period may produce information which will assist materially in assigning the cause of death. The presence of fever is more significant than its absence for all are cognizant of the variability of the febrile response to disease at this age. Similarly, the subnormal temperatures and thermolability of prematures should be taken into consideration. In the first few days of life it is necessary to study the relationship between weight and temperature in order to differentiate between the fevers associated with inanition or dehydration and the ones that are not. Elevations of temperature appearing at birth or shortly after and unrelated to loss of weight probably are the result of birth effects such as intracranial trauma.[61] Fever prolonged beyond the period of initial weight loss is indicative of disease which is either a continuation of the effects of birth trauma or a manifestation of some acquired disease. Neonatal infections such as sepsis or pneumonia are the most common. These conditions are responsible for most of the fever developing late in the neonatal period. Hyperpyrexia is usually associated with high cord injury or massive intracranial or suprarenal hemorrhage.[89]

*Examination of the Placenta.*—The appearance of the placenta at birth may help to explain the cause of fetal death or to foretell the development of later morbidity. It has been stated, and rightly so, that no autopsy in the early days is complete without a thorough examination of the placenta. However, this organ has such a tremendous ability to compensate for diminution of its function that there are only a few lesions of sufficient destructiveness to imperil the life of the fetus.[90] Although the placenta has been studied carefully for years our knowledge about it is still in an unsatisfactory state. Perhaps continued research, especially in respect to nonspecific infections, will yield more satisfactory information about the cause of prematurity and some of the obscure neonatal conditions. So far most placental studies have dealt with obliterative phenomena which may be considered senile degenerative changes developing in a structure having a life span barely sufficient to maintain its physiologic function. The degree of these obliterative changes or infarcts seems to have an effect upon the size and health of the infant. For instance, while there seems to be a close relationship between the size of the placenta and the size of the baby,[91, 92] an oversized placenta is frequently associated with an undersized and underdeveloped infant. These placentas show an exaggerated amount of obliterative change and tend to be associated with maternal toxemias or syphilis.[93] Obstetrical textbooks[94] state that the normal placenta is equal to about one-sixth of the body weight of the fetus and that syphilitic placentas may represent one-fourth to one-half of the fetal weight. In the classical description of this placental disease the organ is pale, and often dull and greasy. The villi lose their arborescent appearance and become thicker and more club shaped. There is a marked decrease in blood vessels due to endarteritis and proliferation of stroma cells. While some recent investigators question the practical value of the his-

tologic diagnosis of syphilis of the placenta,[95-97] especially in premature organs, there remain a large number of observers who consider it of sufficient value to continue its use. It is likely that antisyphilitic treatment of pregnant women has reduced the incidence of the classical histologic picture. It is now generally conceded that an absolute diagnosis rests upon demonstration of spirochetes in the placenta. With maternal toxemia the obliterative changes are increased and edema of the placenta may develop. In cases of congenital hydrops of the fetus the placenta is tremendously large, pale, spongy, and greasy. In a recent case of ours the placenta was over one-half the weight of the fetus. While such changes in the placenta are found in cases of maternal toxemia it does not mean necessarily that placental disease is the causative factor. In other cases the placenta may be large and edematous, the vernix orange colored, and the liquor amnii bile stained. If not already present these findings presage the development of erythroblastosis fetalis which includes icterus gravis and congenital hemolytic anemia. In general it may be said that oversized, pale, edematous placentas containing an excessive number of so-called infarcts should be regarded with suspicion. Histologic studies should be made and spirochetes looked for. Furthermore, blood studies and roentgenograms of the long bones of the fetus are indicated.

### POSTMORTEM PROCEDURES

When it is impossible to obtain autopsy permission use of a number of nonmutilating procedures may assist greatly in determining the correct cause of death. In most instances these examinations should be made immediately after death.

*Roentgenography.*—The roentgenograms have been used too sparingly during neonatal life and but exceptionally after death. Yet this diagnostic method may be of infinite value in determining the cause of death not only in obscure cases but in ones in which the cause seems perfectly obvious. For instance, roentgenograms of the head may reveal an unsuspected skull fracture in an infant manifesting asphyxial symptoms. Intracranial hemorrhage may be detected by injecting opaque material into the arterial system after death. Schoenholz[98] used a solution of minium (red lead) for this purpose. Roberts[99] produced some splendid roentgenograms of intracranial hemorrhage by injecting metallic mercury (30 c.c.). The tendency for mercury to seek the lowest level was the only disadvantage. Use of iodized poppy-seed oil or sodium iodide solution overcomes this difficulty. We have used these solutions satisfactorily for this purpose. Injections may be made into the umbilical vein or carotid artery. Naturally the earlier this is done the better, but we have been able to obtain satisfactory results several hours after death. Absence of radiologic evidence of intracranial hemorrhage will serve to direct the search for the cause of death elsewhere. This method may be used also to detect hemorrhage in other parts of the body. Roentgenography may be utilized after death to detect abnormalities of the thorax. Very little information can be obtained in stillborn infants because there is no tissue differentiation, but after cautious inflation of the lungs identification of thoracic structures is possible.[100] In the infant who has breathed there is sufficient residual air in the lungs to permit differentiation between the lungs, heart, and thymus. However, roentgenograms at this age cannot be interpreted in the same

fashion as in older children.[101-103] Atelectasis is characterized by haziness of the lung fields, the thorax is conical, and the ribs form an acute angle with the vertebral column as compared with a right angle in fully inflated lungs. Pneumonia neonatorum, which is now recognized as a common disease,[104] does not manifest the characteristic roentgenogram found at a later age. Since the pneumonic process is more diffuse and the involved areas small the lung fields usually show a diffuse peribronchial density rather than massive areas of consolidation. The density of the entire lung field is increased and mottling is scattered throughout. Massive collapse of the lung, a not uncommon lesion, is easily demonstrated by x-ray examination. The presence of such rare conditions as pneumothorax, pleural effusions, diaphragmatic hernia, and lung cysts can be detected with little difficulty. Deaths from congenital heart disease are so rare that roentgenography is chiefly of value here in disproving the existence of such abnormalities. It must be remembered that the heart shadow of the newborn infant appears unusually large. This is due to the relatively small size of the chest. Demonstration of an excessively large shadow may be of no significance in the first two days for as Weymuller[102] and his associates have shown there may be a subsequent marked reduction and no indication of heart disease. Persistence of an excessively large heart shadow may indicate some form of congenital heart disease or the so-called congenital hypertrophy of the heart which in all probability is due to myocarditis. The presence of a large thymic shadow is of little significance for it is doubtful whether or not this can be considered a cause of death at this age. Obstruction of the lumen of the alimentary tract may be demonstrated by roentgenogram after injection of opaque material. In case of esophageal atresia the presence of an air bubble in the stomach indicates that there is a communication between the lower portion of the esophagus and the trachea. This can be demonstrated also by injection of barium into the stomach under force whereupon the opaque substance may be seen in the lungs. Roentgenograms are useful to detect evidence of syphilitic periostitis and osteochondritis in the long bones especially in stillborn and newborn infants[105-107] free from external signs of the disease. It is not always possible to charge the death to syphilis for it may be merely an incidental finding. However, frequently syphilis may be indirectly responsible for the lesions causing death. Bony evidence of syphilis may not be demonstrable for several weeks.

*Diagnostic Punctures.*—These procedures may be of nearly as much value shortly after death as they are before death. Bloody spinal fluid suggests the presence of intracranial or cord hemorrhage[108] although it is not always easy to tell whether or not the blood is due to faulty technic.[109] If the red corpuscles are disintegrated or crenated and if after centrifuging the fluid gives a positive benzidine reaction intracranial hemorrhage should be suspected. Cisternal punctures are of more value in this respect because blood from puncture trauma is less likely to be obtained. Yellow-stained cerebrospinal fluid (xanthochromia), especially if it appears early, is hardly to be considered definite evidence of old intracranial hemorrhage. According to a number of investigators this phenomenon is physiologic and especially is this true of fluids obtained from premature infants. Levinson considers xanthochromia associated with a positive benzidine reaction indicative of cerebral hemorrhage.[110] In case of ventricular hemorrhage cerebrospinal

fluid may appear normal unless ventricular puncture is performed. Bacteriologic examination of the spinal fluid will sometimes reveal the presence of an unsuspected meningitis, and serologic studies may demonstrate a syphilitic infection. Thoracentesis should be performed when pleural exudates or hemorrhage is suspected and lung punctures done under sterile precautions may yield fluid which after culture will reveal the presence of pulmonary infection. Abdominal puncture followed by aspiration of some of the contents of the peritoneum is of value in diagnosing intraperitoneal hemorrhage or peritonitis. Aspiration of heart's blood is a procedure which should be used more frequently. Blood cultures obtained from this source will reveal the presence of a blood stream infection more often than one would suspect. Blood Wassermann tests should be made although it must be realized that positive reactions at this period of life are not always significant. Sometimes there is a transitory positive Wassermann due to transference of antibodies from an infected mother to an uninfected child.[111, 112] Occasionally nonspecific reactions occur. For this reason corroborative evidence of syphilis should be looked for. This includes roentgenography and dark field examination of the fluid obtained from gland puncture or puncture of the liver or spleen. Cytologic examination of the blood may help to identify some of the deaths due to the blood dyscrasias. Anemia of the idiopathic sort or erythroblastosis may be differentiated in this way.

## SUMMARY

Use of some of the procedures mentioned above as well as careful perusal of prenatal, labor, and neonatal records will go a long way toward making neonatal statistics of more scientific value. It seems incredible that physicians who search so enthusiastically and tirelessly for the cause of death in adults and children will assume such an indifferent attitude in respect to neonatal death. Until this situation is corrected mortality statistics for this age group cannot be analyzed accurately. Their relative inaccuracy has been admirably shown in the recent report of Bundesen[113] and his associates. When deaths certified according to the International List were compared with deaths checked by autopsy they found a striking disparity in the frequency and importance of certain causes of death.

Correction of the conditions responsible for inaccuracies in recording neonatal deaths is dependent upon several factors:

1. Revision of the International List of Causes of Death so that ambiguous and misleading headings which serve as catchalls for obscure deaths may be deleted.

2. Adherence of teachers to such a revised list or some other satisfactory one so that more uniformity of recording deaths may be brought about.

3. Increased interest in trying to ascertain the cause of neonatal death. This, of course, means a greater number of autopsies.

4. Intensive study of neonatal pathology and physiology with the idea of clarifying much of the confusion that exists in respect to disease at this age.

Until all this is accomplished it will be difficult to evaluate the importance of the various factors responsible for the present high and unyielding newborn infant death rate. It will be possible then to determine

with greater accuracy which deaths are preventable and institute corrective measures. Accumulating evidence points with greater certainty to the fact that these deaths, many of which are preventable, may be classed as obstetric deaths. While birth trauma may be the important factor many times one should not overlook the fact that antenatal conditions affecting the physical integrity of the fetus may be indirectly responsible.[114] It is evident then that there is a distinct need for more research in antenatal and natal problems. Bundesen is correct in stating that the baby as well as the mother is entitled to skilled care during pregnancy and labor. The proper solution of the entire problem seems to the reviewer to lie in the establishment of one or more institutions devoted solely to intensive and coordinated study of these problems.

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# American Academy of Pediatrics

## Proceedings

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3, 4, AND 5, 1937

**Round Table Discussion on Treatment of Empyema**

Chairman: Dr. Edward J. Donovan, New York, N. Y.

Assistants: Dr. Frank B. Berry, New York, N. Y.
Dr. William G. Heeks, New York, N. Y.

### The Surgical Treatment of Empyema of the Thorax in Children

Edward J. Donovan, M.D.

The surgical treatment of an empyema of the thorax in a child may be one of the most difficult tasks that the surgeon encounters, and the accomplishment of his purpose may tax his ability to the utmost. By the time the empyema cases reach the surgeon the patients' resistance may be at its lowest ebb, they may be undernourished, dehydrated and toxic because they have passed through some serious illness such as pneumonia, before the empyema develops. As a group they are poor surgical risks and must be treated carefully, especially during the acute phase of the disease or the mortality, which is still too high, will be much greater. It is my purpose today to review briefly the subject of the surgical treatment of empyema in children and to outline in a general way the method as we carry it out at the Babies Hospital.

An empyema may be either diffuse or sacculated; in the former the pressure of the exudate is exerted upon all sides of the lung equally. In the sacculated type, which is the type seen most often, the pressure of the exudate may compress the lung in one or more places but there is still a certain portion of the lung free from this pressure and therefore capable of functioning. The most common location of empyema in children is in the posterolateral portion of the chest and may be drained through the eighth interspace in the posterior axillary line.

The infection may reach the pleura (1) by the blood stream, in which case the empyema is just one manifestation of the general sepsis, (2) by the lymphatics from a neighboring focus, (3) by the rupture of an extrapleural abscess into the thorax, (4) rupture of a subpleural or a subcortical abscess into the pleural cavity during pneumonia. The latter is by far the most common cause.

Many organisms have been found to cause an empyema, but in the majority of cases the infecting organism is either a pneumococcus or the *Streptococcus hemolyticus*. In pneumococcus empyema the pus is usually thick, contains more fibrin and therefore will become walled off more quickly than the streptococcus type where the pus is apt to be much thinner, present in greater quantity, and to contain much less fibrin. This walling off process is very important in the surgical treatment since it allows the mediastinum to become stabilized and the lung fixed to the chest

wall and diaphragm, very important requisites before open thoracotomy is done. If the lung collapses when the chest is opened, a simple empyema is converted into a pyopneumothorax.

The diagnosis of empyema usually denotes a history of a recent respiratory infection, signs of fluid in the chest, and the characteristic x-ray appearance of pleural exudate. The diagnosis is confirmed by exploration of the chest with a needle. A specimen of the pus obtained should always be saved for the surgeon to see, as its gross appearance is often helpful to him in determining the course of treatment he wishes to establish. If the pus is thick and creamy it usually means that the chest is ready to be drained, if the patient's condition warrants it. Smear and culture of the pus should always be done as the identification of the causative organism is often a deciding factor in the surgical treatment.

Exploration of the chest with a needle should not be taken too lightly; it should be done under the most aseptic precautions and done only when there is sufficient evidence to warrant it. The procedure carries the following dangers, (1) hemorrhage from an intercostal vessel, particularly if a large needle is used, causing either a hematoma of the chest wall or a hemothorax, (2) air embolism, (3) infection of the chest wall when the needle is withdrawn from an infected focus in the chest, (4) puncture of the diaphragm, (5) production of a pneumothorax, (6) carrying infection into the clean pleura from the outside.

With the diagnosis made the further procedure of the surgeon depends, first upon the general condition of the child, and secondly upon the quantity and the character of the pus obtained by puncture. If the patient is in great distress from the quantity of pus present, the heart displaced, etc., the best procedure is to aspirate the chest, taking off only enough pus for relief. This process may be repeated several times if necessary. Major surgical procedures are contraindicated under such circumstances and are entirely unnecessary. The fact that pus is present in the chest does not mean immediate operation. If the pus accumulates rapidly and you are not sure that the process in the chest is walled off, do a closed drainage. This simple apparatus may be applied under local anesthesia without disturbing the patient in the least. There are many other advantages of closed drainage besides its simplicity of application, namely (1) the rate of drainage is directly under the surgeon's control, (2) being air-tight it helps the lung to expand, (3) if irrigation of the chest seems to be advantageous, it may easily be done with this apparatus. Closed drainage will remain air-tight for from five to eight days at the end of which time friction of the tube in the chest causes leakage. By this time we may feel quite safe in establishing open drainage as we are quite sure that the process is walled off. The simplest way to accomplish this is to cut off the present drainage tube about three-quarters of an inch outside the chest wall and put a safety pin in it. Open drainage of this type is adequate for about a week or ten days, at the end of which time the patient has improved sufficiently to have a rib resection if necessary. The indications for removing a rib at this time are proof that the chest is not adequately drained as shown by the temperature and by an x-ray picture of the chest. If it is necessary to resect the rib we usually remove one and one-half inches of the eighth rib in the posterior axillary line, under avertin with local novocaine block of the rib to be removed. If the temperature is normal patients are allowed out of bed one week after rib resection. All cases have a daily dressing or an inspection of the incision once a day. The drainage tubes are not removed until drainage ceases or until we are satisfied that the chest is properly drained. After removal of the drain tube the sinus is kept open for at least a week by inserting a catheter into the chest for a few moments each day when the dressing is changed. Blow bottles, playing the harmonica, etc., are useful measures to help the lung to expand after the drainage tubes are out. We do not use irrigation with antiseptic solution in the treatment of empyema in children except in an occasional case

where there is a great deal of fibrin present. We prefer Dakin's solution when we do use one, but feel that the use of these solutions is unnecessary in children if drainage of the chest is properly carried out.

Prontylin and prontosil may be very useful in the treatment of streptococcus empyema. We have not used them simply because we have not had a good case in which to try them. We have used these preparations very successfully in three cases of streptococcus peritonitis and hope that we may find them as helpful in the treatment of empyema.

During the course of the surgical treatment as outlined above, it is necessary to (1) restore the patient to his normal health as soon as possible. High caloric diet, sunshine and fresh air are very helpful in accomplishing this. (2) Watch the patient's posture while in bed. We send them to the posture clinic as soon as they are able to go and find most of them are only too eager to cooperate in doing the exercises prescribed for them. As soon as we are able, we send the empyema cases to the country to complete their convalescence. They thrive there as no other group does. In a short time they have gained weight and soon reach a point where they might have been had they not had empyema.

The aim of the surgeon in treating an empyema in a child should be to drain the chest thoroughly, just as quickly as it is consistent with the child's general condition. We believe in being very conservative during the acute phase of the disease and try to bear in mind the fact that the margin of safety is very small in many of these patients. We believe that there are practically no cases of empyema so acute as to require major surgical procedures to be done as emergencies during the acute part of the disease.

Generally speaking, an empyema is a very serious condition for any child to stand and particularly when he has been depleted by some other serious illness before the empyema developed. The mortality in general varies, therefore, inversely with the age of the child. Under two years of age it is very high but should decrease rapidly with each year's increase in age. Autopsy reports show that the complications of empyema have more influence on the mortality than the empyema itself.

## Notes on Physiology of Respiration

Frank B. Berry, M.D.

In order to treat empyema intelligently a true conception of the anatomy, physiology, and mechanics of the lungs and cardiorespiratory balance is necessary. It should always be our aim, as far as possible, to restore and maintain the normal relationships and balance within the chest in the manner least harmful to the patient. Graham and his coworkers have demonstrated very clearly the effect of open pneumothorax and resultant mediastinal shift both in the healthy individual and in the patient ill with pneumonia and empyema. He has further pointed out the difference between synpneumonic and metapneumonic empyema. In the former, the fluid is thin, develops early, rapidly, and in large amounts. This results in marked dyspnea with rapid and shallow breathing, interference with the normal respiratory gas exchange, pressure on the mediastinal structures with torsion of the heart and vessels, and is usually extremely toxic. The lung damage per se may be relatively slight, but there has been great impairment of the mechanics of respiration, with marked diminution in vital capacity and reserve air. This disturbance may be, and frequently is, so great that drainage by open thoracotomy cannot be tolerated and the patient will die because, in the absence of protective adhesions at such a time, an inrush of air will diminish still further the already greatly reduced cardiorespiratory and pulmonary reserve. It is in such instances that repeated aspirations or closed drainage, as prescribed by Dr. Donovan, are not only indicated but are indeed a life-saving procedure. By such a method the patient is not disturbed and yet sufficient has been accomplished to establish drainage and allow the heart and lungs

to return gradually to their normal positions and resume their normal functions. Only later, where the fluid has become thick and protecting adhesions have formed is open thoracotomy indicated, and then it is not only safe but is distinctly advisable and should not be delayed, unless it is evident that the empyema is clearing and the cavity steadily diminishing in size. At this time, the mediastinum is fixed and stable, the patient is over his acute illness and vital capacity and reserve air have been largely restored to their normal status. At this time then, open thoracotomy need not be feared and should be performed at the most dependent portion of the empyema cavity if pus continues to accumulate after two or three weeks of closed drainage, or if the lung fails to reexpand. Otherwise, the development of chronic empyema is favored. Drainage should be maintained until the cavity holds 10 c.c. or less, so as not to leave a potentially infected pneumothorax. An empyema is cured only when the cavity is obliterated and the lung is once more in apposition with the chest wall—its normal position.

## Statistics on the Surgical Treatment of Empyema at the Babies Hospital With Brief Reports on Some of the Interesting Complications Encountered

William G. Heeks, M.D.

In the period from Dec. 1, 1929, to Jan. 1, 1935, there are records of 119 cases of acute suppurative pleurisy at the Babies Hospital. In this entire group there were 19 deaths, a mortality rate of 16.0 per cent. However, in analyzing the case histories of those who died, it was obvious that 9 should be excluded inasmuch as this paper deals only with cases treated surgically. With this correction, there remain to be considered 110 cases with 10 deaths, a mortality rate of 9.1 per cent.

Table I correlates the number of cases and deaths by years.

TABLE I

NUMBER OF CASES AND DEATHS BY YEARS

| AGE YEARS | NUMBER OF CASES | PER CENT OF TOTAL CASES | NUMBER OF DEATHS | PER CENT OF DEATHS BY YEARS | PER CENT OF TOTAL DEATHS | DEATHS PER CENT TOTAL SERIES |
|---|---|---|---|---|---|---|
| 0 to 1 | 16 | 14.5 | 5 | 31.2 | 50.0 | 4.5 |
| 1 to 2 | 20 | 18.2 | 4 | 40.0 | 40.0 | 3.7 |
| 2 to 5 | 38 | 34.6 | 1 | 2.6 | 10.0 | 0.9 |
| 5 to 12 | 36 | 32.7 | 0 | 0.0 | 0.0 | 0.0 |
| Total | 110 | | 10 | | | 9.1 |

From a study of this table and other published series I would summarize my conclusions as follows. Respiratory infections vary in type and virulence in different localities and in the same locality in different years. The pathologic conditions to which they give rise may be a simple empyema or one associated with other serious conditions. The mortality varies in different age groups, in different types of infections, in different localities, and in different years, and these variations in the mortality are dependent in greater degree upon the incidence of pathologic conditions other than empyema than upon the empyema itself or the kind of operation performed, provided established surgical principles are followed.

### CASES PRESENTING UNUSUAL COMPLICATIONS

CASE 1.—Pneumonia with early massive effusion, ultimate death from metastatic brain abscess.

M. S., a white male child of nine years, was admitted in October, 1935, with a history of one hour previously having had a bad coughing spell accompanied by sharp pain in the chest. He had been in the hospital one year before at which time a diagnosis of bronchiectasis was made, otherwise the past history was unessential.

The day following admission the child was acutely ill and examination revealed a diffuse pneumonia on the left with a question of a large effusion. The second day the chest was bulging from the large amount of fluid and a thoracentesis was done. The fluid was thin and a culture grew hemolytic streptococci. His course was uneventful and thirteen days later a rib resection was performed. At this time the fluid was fairly thin but a large amount of thick exudate was on both parietal and visceral pleura. The lung was partially collapsed.

He did exceedingly well for the next ten days when suddenly he had a series of convulsions and complained of severe headache. A neurologic examination suggested brain abscess. A spinal puncture revealed clear fluid under increased pressure and cultured hemolytic streptococci.

Autopsy revealed: Chronic interstitial pneumonia and abscess of the brain in the left cerebral hemisphere with rupture into the lateral ventricle. Culture from the abscess grew hemolytic streptococci.

CASE 2.—Pneumonia with massive pleural effusion; pericarditis with effusion; eventual thoracotomy; failure of lung to reexpand; institution of water suction with eventual good result.

F. M., a white female of seven years, was admitted on Jan. 4, 1935, having been ill at home with pneumonia since December 23. The child was acutely ill, in respiratory distress and the lips were cyanotic. There was a marked effusion on the right, the heart widely displaced, and a to-and-fro friction rub was heard over the precordium. A thoracentesis was done, removing 350 c.c. of cloudy fluid which cultured pneumococcus Type 5. On January 5, a closed siphon drainage was instituted. On January 14, a pneumothorax was present, little fluid was seen, the lung was collapsed, the trachea displaced to the left, and the area of cardiac dullness greatly enlarged.

February 9, bronchoscopy revealed a collapsed lung; several primary bronchi were seen and there was no plugging. At this time the patient had a severe deformity of the chest; a left scoliosis was present with retraction of the lower sternal region. Physiotherapy was instituted.

March 6 a thoracotomy was done and the thick visceral pleura incised and cross-hatched. No pus was present. There was no evidence of a bronchopleural fistula. The lung reexpanded only slightly. May 6 a rubber tube was inserted and water suction was applied using a pressure of 12 cm. of water. This was allowed to remain two weeks, and a simple open rubber drainage tube left in place for another ten weeks following which the wound was allowed to close. Good reexpansion was secured. Aug. 16, 1936, the wound was well healed and the child was symptom free. There remained only a slight scoliosis which was flexible and could be corrected by bending.

A series of x-ray films showing the progress of this case are shown and also a diagram of the method used in obtaining negative intrapleural pressure by water suction.

CASE 3.—Sequestration of the right upper lobe in the course of empyema; recovery with persistent pneumothorax.

Veronica M., a white female of five years, was admitted June 11, 1932, with pneumonia and empyema of the right chest, already detected by thoracentesis by the family doctor. Closed drainage was instituted followed by simple intercostal drainage and later by rib resection. The organism was a pneumococcus, Type 1. Because of signs of inadequate drainage, a second thoracotomy with rib resection was

performed a month after the first. A small amount of pus was found in the pleural cavity. Examination of the lung showed practically a complete collapse of the entire right lung with a piece of tissue, roughly oval and flattened loosely, adherent to the region of the hilum and in reality quite free. It came away so readily when grasped with sponge forceps that it was difficult to appreciate any adhesions between it and the hilum. Moreover there was no bleeding following removal of the mass, and on sponging out the pleural cavity the walls appeared dry and fairly clean. Pathologic examination revealed the mass to be necrotic lung. The child was discharged four and one-half months after admission with the wound practically healed.

The child was readmitted March 26, 1934, with an upper respiratory infection. Gradually fluid collected and a pyopneumothorax was diagnosed. April 9, 1934, two ribs were partially resected at the site of the old operation and the pus evacuated. Convalescence was uneventful.

This patient was last examined in March, 1937, at which time all wounds were soundly healed, there were no respiratory complaints and her general condition was excellent.

I have a series of lantern slides demonstrating the x-ray findings throughout the course of the disease and also two photographs of the sequestrated lung.

## DISCUSSION

DR. FRANK B. BERRY (NEW YORK, N. Y.).—My personal experience has mostly been with adults; however, the principles of treatment and physiology are the same for adults and children. The pleurae and mediastinum are not fixed as shown by Graham and colleagues during the World War.

Pressure in the chest is normally -5 to -9 mm. water in expiration and inspiration.

The most common organisms causing empyema are the streptococcus and pneumococcus.

In all pneumonias there is a certain increase in the fluid within the pleural cavities. If this fluid increase is rapid and early in the course of the disease it produces very serious disability, the child becoming toxic, cyanotic, and dyspneic. Both the vital capacity and reserve air are much reduced with the result that the physiologic balance is easily upset. The normal lung is compressed by the diseased lung while the movable mediastinum is subjected to shift.

When the above signs of increased pressure within one pleural cavity are noted aspiration must be done as an emergency measure. Only sufficient fluid should be aspirated to relieve the patient. A too complete aspiration may be very dangerous and even result in death.

When streptococcus empyema was operated early by the open method the mortality ranged between 40 and 50 per cent. With the introduction of the closed method there was an immediate drop to around a 15 per cent mortality.

Late operation after the empyema becomes a localized abscess is greatly simplified in that complete drainage is the only necessary condition to be met.

The commonest organisms causing empyema in very young children are the streptococcus and staphylococcus while in older children a greater number are caused by the pneumococcus.

DR. CLEMENT B. P. COBB (NEW YORK, N. Y.).—I have heard that prontolyn has not been useful in the treatment of streptococcus empyema. The following are observations on two cases so treated without evident effect.

DR. DOUGLAS P. ARNOLD (BUFFALO, N. Y.).—Is the dosage used which was given by Long and Bliss?

DR. COBB.—A massive first dose was not given. Three-tenths gram was given every four hours the first twenty-four hours, and every six hours the second. Treatment was considered to be without appreciable effect, though it was persisted in for several days.

CHAIRMAN DONOVAN.—The first infant mentioned above, who had peritonitis became jaundiced. The prontosil was stopped because of the jaundice but when the number of colonies obtained by blood culture increased from 100 to 1,400 it was started again and continued until recovery occurred.

DR. ARTHUR HEYMAN (NEWARK, N. J.).—I would like to have the technique for inserting the mushroom catheter explained again.

CHAIRMAN DONOVAN.—An incision just large enough to carry the tube is made in the intercostal space in the posterior axillary line down to the pleura. The tube is then inserted with a mosquito forceps clamped over the end. The clamp is removed and the tube allowed to drain. The free end of the tube is submerged in water in order to keep the system of drainage a closed one, and if the fluid tends to escape too rapidly, the tube should be clamped off from time to time. Occasionally this type of drainage will not work because of large quantity of fibrin present which blocks the tube. If an irrigation seems necessary, normal saline is preferred. We do not believe that irrigations with antiseptic solutions are necessary in the treatment of empyema in children.

DR. WILLIAM F. BURDICK (WASHINGTON, D. C.).—I am not a surgeon but I believe that, even with the use of prontolyn, wherever there is pus in a closed cavity it should be drained. I have seen prontolyn have a very marked favorable effect on draining ears and cervical adenitis.

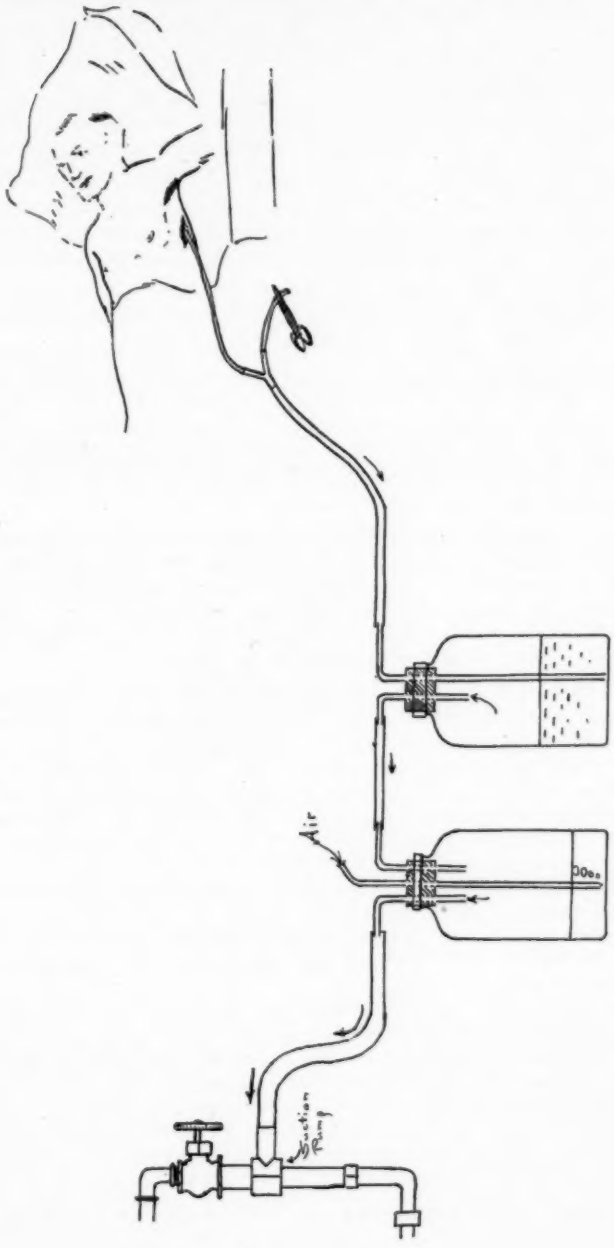
DR. JACOB ROSENBLOOM (BROOKLYN, N. Y.).—The army experience has taught us that empyema is not an emergency operation. An empyema that cannot wait for operation is one of bad prognostic omen. When the child appears desperately ill it is, as a rule, due to the underlying pneumonic process rather than the superimposed pleural effusion. These children obtain greater relief in an oxygen tent than after aspiration of pleural fluid. Occasionally, especially in infants, aspiration of a synpneumonic empyema may be necessary for relief. A rupture of a pleural abscess with the formation of a sudden pyopneumothorax may require rapid and urgent intervention. These cases, however, are rare. All the rest of the empyema cases can wait. It is our procedure to wait at least seven days after the pneumonic process has terminated before instituting drainage. When the pneumonic process is over, the general condition continues to improve in spite of the increase of fluid in the pleural cavity. When the general condition is good, operation is performed. During the interval the child is not disturbed. Diagnostic chest punctures are omitted.

The closed method is the one that has given us the most satisfactory results and we have used it almost exclusively.

After drainage has been established the question of reexpansion of the lung must be considered, as this is the most important single factor in the obliteration of the cavity. To hasten obliteration of the cavity I have suggested the introduction of an artificial pneumothorax on the unaffected side. The details of this method and the reasons for it have been reported in the *Journal of the American Medical Association* of April 27, 1935.

WILLIAM G. HEEKS (NEW YORK, N. Y.).—Mortality statistics should always be arranged by age groups. Also upon the type of empyema.

DR. ARNOLD.—Why wait to institute closed drainage?


Air
Suction Pump

DR. BERRY.—I have used prontolyn. Beck has shown that the heart can withstand traction in the long axis but if the heart is moved laterally or is twisted there is an immediate alarming fall in blood pressure. This explains the grave danger of too rapid removal of fluid during an early empyema which is not well walled off.

DR. CLIFFORD SWEET (OAKLAND, CALIF.)—I have seen some infants recover from empyema by means of repeated aspiration only. However, recovery has been slow and it seems to me closed catheter drainage should replace aspiration unless recovery is very rapid.

DR. HEEKS.—I have not seen a case of empyema recover with repeated aspiration alone. A catheter introduced for closed drainage should not be left in place too long. That is, when recovery is not evidently proceeding satisfactorily rib resection should be done.

DR. SWEET.—Is there any objection to the use of the trocar as a means of introducing the catheter into the empyema cavity?

CHAIRMAN DONOVAN.—No. One may use the method with which he is familiar.

DR. SWEET.—Dr. Donovan says the closed drainage remains air-tight for only five to eight days. Ours have remained air-tight for a much longer time than this. I wonder if the trocar method may not offer the advantage of the drainage remaining closed for a longer time?

Doctors Donovan, Berry, and Heeks have made very clear that closed drainage established by introducing a catheter into the empyema cavity between the ribs is not to be thought of as a substitute for rib resection and ample open drainage but rather as the surgical treatment of choice in early empyema. This simple relatively safe method of drainage may be all that is necessary but if recovery does not take place rib resection can then be done much more safely.

DR. ARNOLD.—I agree with the method for the treatment of empyema outlined by Doctors Donovan, Berry, and Heeks. They are essentially the methods used in the treatment of empyema at the Buffalo Children's Hospital.

I am certain that physicians generally, do not realize the dangers of early open drainage and the advantages of the closed method. The question is: what can we do to make them realize that they must not do an open rib resection until the pus is thick enough? An early rib resection during the acute illness and when the pus is thin is often fatal.

I wish to call attention to the successful treatment of streptococcic empyema with sulfanilamide given by mouth. This is to be used in large doses as advised by Long and Bliss so that the concentration in the blood is about 10 mg. per cent. When this cannot be used by mouth, sulfonamide in a 0.8 per cent saline solution can be used by clysis.

Doctor Sweet, with your permission, I will show three charts of streptococcic empyema treated with prontolyn by mouth; in these cases the culture of the pus became sterile within three or four days and the children made an uninterrupted recovery. In two cases, only enough fluid was removed for culture; in the first case, a quantity of fluid was evacuated by aspiration.

This seems to be a great advance in the therapy of streptococcic empyema and as it appears at present, it may render surgery unnecessary in this particular type of infection.

CHAIRMAN DONOVAN.—Children two years of age and older should not die from empyema if the treatment is conservative.

Streptococcus empyema treatment contrasted with pneumococcus.

DR. CHARLES S. NORBURN (ASHEVILLE, N. C.).—How often is rib resection necessary after closed drainage?

DR. HEEKS.—Of all those patients at Babies Hospital who were treated with closed drainage, only 5 per cent recovered without rib resection.

DR. W. L. CHADWICK (GRAND RAPIDS, MICH.).—How long is closed drainage usually continued before rib resection?

CHAIRMAN DONOVAN.—Syphon closed drainage is continued not longer than ten to fourteen days to prevent pressure necrosis around the tube. Children under five years of age are practically the only age group who ever completely recover without final rib resection.

DR. CHARLES S. LIPSITT (NEW BEDFORD, MASS.).—How long is aspiration usually continued before instituting closed drainage?

CHAIRMAN DONOVAN.—Aspirate until there is no doubt in your mind about its being time for more radical procedure. Indications for insertion of tube are: (1) the amount of fluid present; (2) the character of fluid present; (3) the degree of respiratory distress occasioned by the presence of the fluid.

I have not seen a case of empyema recover with repeated aspiration alone. A catheter introduced for closed drainage should not be left in place too long. That is, when recovery is not evidently proceeding satisfactorily rib resection should be done.

DR. WARD L. CHADWICK (GRAND RAPIDS, MICH.).—What dosage of avertin have you found necessary?

CHAIRMAN DONOVAN.—85 to 100 mg. of avertin, then infiltrate locally with novocain.

DR. NORBURN.—Does the substitution of normal saline solution for the amount of pus removed, save some patients from disturbing pressure symptoms?

CHAIRMAN DONOVAN.—Yes, sometives even air injected into the pleural cavity may save the patient from having a severe reaction, especially when too much fluid has been removed in one aspiration.

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# Academy News

The four regions of the Academy will hold fall meetings as follows:

Region I will meet in Boston, Mass., on Nov. 12 and 13, 1937. The program on Nov. 12 consists of a symposium, "Certain Relations of Vitamin C to Nutrition," also a clinical demonstration, "The Effects of Anemia on Growth." In the afternoon, papers will be presented by local members. On Saturday, November 13, there will be a symposium, "Functional Anomalies in Vision of Children," to be given by members of the staff of the Massachusetts Eye and Ear Infirmary and by the Department of Ophthalmology of the Harvard Medical School. On Saturday afternoon one-hour demonstrations will be given in the form of round table discussions on various clinical conditions in children. Arrangements have also been made for a visit to the Wrentham Hospital for a presentation of a group of mentally defective children uniquely classified.

Headquarters will be at the Coply Plaza Hotel. The demonstrations will be held at the Harvard Medical School. It is requested that reservations at hotels and arrangements for attendance be made as soon as possible.

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Region II will meet jointly with the **Pediatric Section of the Southern Medical Association** at New Orleans, La., on Dec. 1 and 2, 1937. The program on the opening day, December 1 will consist of four panel discussions, "Allergy," "Whooping Cough Immunization," "Mental Health in Childhood," and "Poliomyelitis." On December 2 there will be clinical presentations by local pediatricians.

The business meeting of Region II will be held at 11:00 o'clock December 2. Several important matters of the Academy will be presented for discussion.

The afternoon sessions will be devoted to section meetings. Reservations for rooms may be had at the Jung Hotel which will be unofficial headquarters.

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Region III will meet in Chicago, Ill., on Oct. 14, 15, and 16, 1937. Headquarters will be at the Lake Shore Athletic Club, 850 Lake Shore Drive where reservations should be made. On Thursday, October 14 the sessions will be held in the morning at Presbyterian Hospital. The afternoon session will be held at the Cook County Children's Hospital after luncheon at the Cook County Nurses Home.

A reception will be held at the Lake Shore Athletic Club at 6:00 P.M. by members of the **Chicago Pediatric Society.** Following dinner, there will be various business meetings.

On Friday, October 15 the sessions will be held in the morning at Bobs Roberts Memorial Hospital where luncheon will be served at 12:30. The afternoon session will be held at Sarah Morris Hospital. A diner dance is arranged for 8:00 P.M. on October 15 at the Lake Shore Athletic Club.

The morning session on Saturday, October 16 will be held at the Children's Memorial Hospital with reports and clinical presentation of cases by members of the staff. Luncheon will be served at the Hospital at 12:30.

After adjournment, members may attend the Northwestern University-Purdue University or Chicago University-Princeton University football games.

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The annual meeting of Region IV will be held at Los Angeles, Calif., on Nov. 4, 5, and 6, 1937. The headquarters for all scientific programs, as well as for special meetings and extra events will be at the Ambassador Hotel.

This year, instead of being presented exclusively by the local members, the program will include three groups: Papers presented by members scattered over the entire Region; presentations by guest speakers who have material of exceptional merit; and, of course, a group of papers by local members.

It appears that there will be features on allergy and endocrinology of unusual interest.

Entertainment high lights sound attractive and the meeting will, following tradition, wind up with the Stanford University-University of Southern California football game.